*Doc. No. TFDA/DMC/HVR/G/001*

**TANZANIA FOOD AND DRUGS AUTHORITY**

# GUIDELINES ON THERAPEUTIC EQUIVALENCE REQUIREMENTS

*(Made under Section 52 (1) of the Tanzania Food, Drugs and Cosmetics Act, 2003)*

**First Edition**
**January, 2015**

P. O. Box 77150, EPI Mabibo, Off Mandela Road, Dar es Salaam, Tanzania
Tel: +255-22-2450512/2450751/ 2452108; Fax: +255-22-2450793
Email: info@tfda.or.tz; Website: **www.tfda.or.tz**

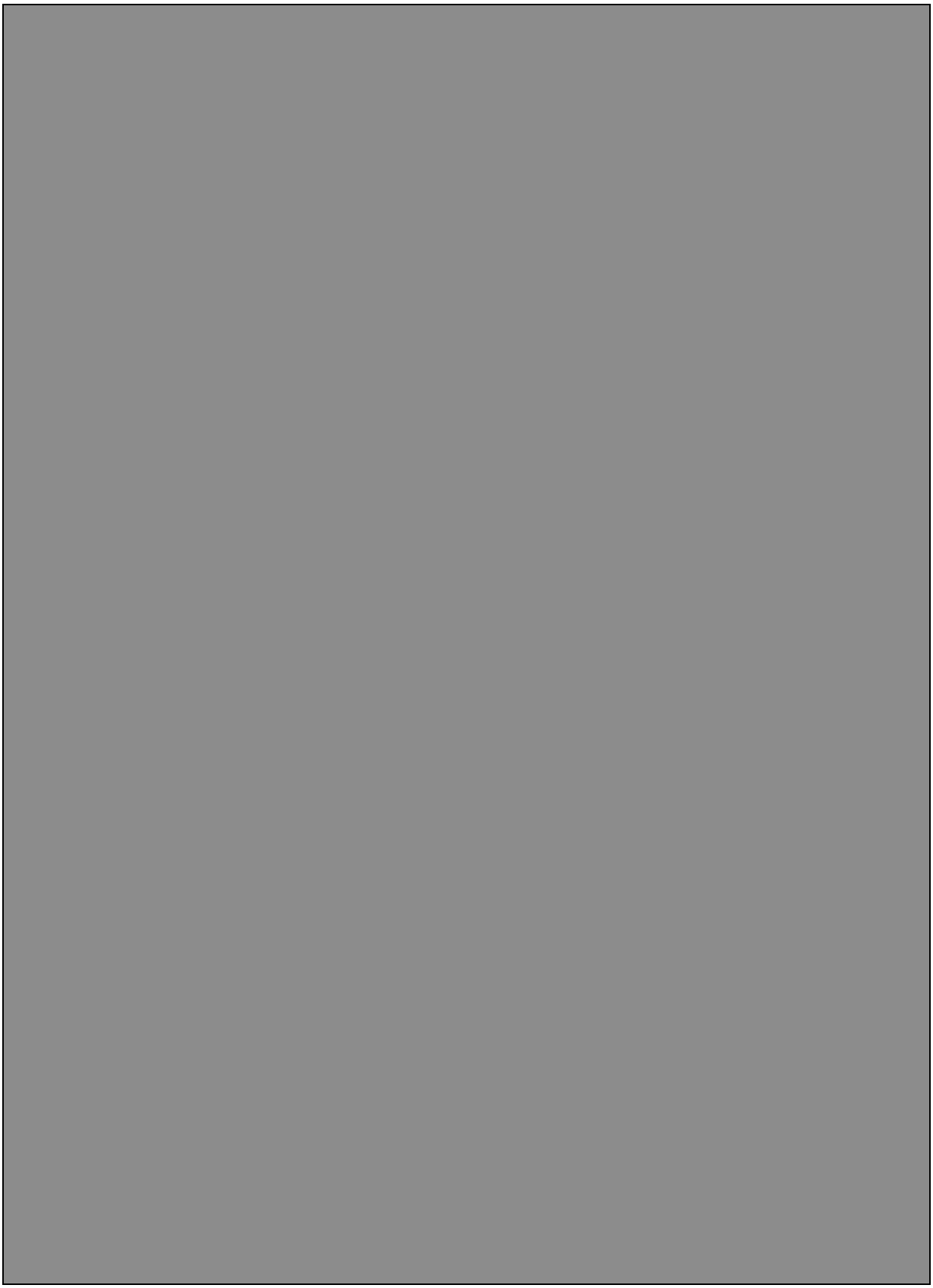

**TABLE OF CONTENTS**

**ABBREVIATIONS AND ACRONYMS**

| | |
|---|---|
| BCS | Biopharmaceutics Classification System |
| $f_2$ | Similarity factor |
| GCP | Good Clinical Practice |
| $Ae_{(0-t)}$ | Cumulative urinary excretion of unchanged drug from administration until time t; |
| $AUC_{(0-t)}$: | Area under the plasma concentration curve from administration to last observed concentration at time t; |
| $AUC_{(0-\infty)}$: | Area under the plasma concentration curve extrapolated to infinite time; |
| $AUC_{(0-\tau)}$: | AUC during a dosage interval at steady state; |
| $AUC_{(0-72h)}$ | Area under the plasma concentration curve from administration to 72h; |
| $C_{max}$: | Maximum plasma concentration; |
| $C_{max,ss}$: | Maximum plasma concentration at steady state; |
| residual area | Extrapolated area ($AUC_{(0-\infty)}$ - $AUC_{(0-t)}$)/ $AUC_{(0-\infty)}$; |
| $R_{max}$ | Maximal rate of urinary excretion; |
| $t_{max}$: | Time until $C_{max}$ is reached; |
| $t_{max,ss}$: | Time until $C_{max,ss}$ is reached; |
| $t_{1/2}$: | Plasma concentration half-life; |
| $\lambda_z$: | Terminal rate constant; |
| SmPC | Summary of Product Characteristics |

**DEFINITIONS**

**Absorption** - the uptake of substance from a solution into or across tissues. As a time dependent process; absorption can include passive diffusion, facilitated passive diffusion (with a carrier molecule), and active transport. A Pharmaceutical product is considered to be highly absorbed when the measured extent of absorption of the highest therapeutic dose is greater or equal to (≥) 85%. High absorption: ≥ 85% of the administered dose absorbed.

**Active moiety (Active):** is the term used for the therapeutically active entity in the final formulation of a medicine, irrespective of the form of the API. The active is alternative terminology with the same meaning. For example, if the API is propranolol hydrochloride, the active moiety (and the active) is propranolol.

**Active Pharmaceutical Ingredient (API):** A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a therapeutically active ingredient.

**Bioavailability:** refers to the rate and extent to which the API, or its active moiety, is absorbed from a pharmaceutical product and becomes available at the site of action. It may be useful to distinguish between the "absolute bioavailability" of a given dosage form as compared with that (100 %) following intravenous administration (e.g. oral solution *vs.* intravenous), and the "relative bioavailability" as compared with another form administered by the same or another non-intravenous route (e.g. tablets vs. oral solution).

**Bioequivalence:** Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and if their bioavailabilities in terms of peak ($C_{max}$ and $T_{max}$) and total exposure (AUC) after administration of the same molar dose under the same conditions are similar to such a degree that their effects with respect to both efficacy and safety can be expected to be essentially the same. Bioequivalence focuses on the equivalence of release of the active pharmaceutical ingredient from the pharmaceutical product and its subsequent absorption into the systemic circulation. Comparative studies using clinical or pharmacodynamic end points may also be used to demonstrate bioequivalence.

**Biopharmaceutics Classification System (BCS)**-based biowaivers are meant to reduce the need for establishing *in vivo* bioequivalence in situations where *in vitro* data may be considered to provide a reasonable estimate of the relative *in vivo* performance of two products. The BCS is a scientific approach designed to predict medicinal absorption based on the aqueous solubility and intestinal absorptive characteristics of the Pharmaceutical product.

**Biowaiver:** The term biowaiver is applied to a regulatory drug approval process when the dossier (application) is approved based on evidence of equivalence other than through in vivo equivalence testing.

**Comparator product:** is a pharmaceutical product with which the generic product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product for which efficacy, safety and quality have been established.

**Critical dose medicinal** - Medicinal product where comparatively small differences in dose or concentration lead to dose- and concentration-dependent, serious therapeutic failures and/or serious adverse medicinal reactions which may be persistent, irreversible, slowly reversible, or life threatening, which could result in hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, or death. Adverse reactions that require significant medical intervention to prevent one of these outcomes are also considered to be serious.

**Dose solubility volume (DSV)** - the highest therapeutic dose [milligram (mg)] divided by the solubility of the substance [milligram/milliliter (mg/mL)] at a given pH and temperature. For example, if a Pharmaceutical product has a solubility of 31 mg/mL at pH 4.5 (37°C) and the highest dose is 500 mg, then DSV = 500 mg/31 mg/mL = 16 mL at pH 4.5 (37°C).

**Fixed-dose combination (FDC):** A combination of two or more active pharmaceutical ingredients in a fixed ratio of doses. This term is used generically to mean a particular combination of active pharmaceutical ingredients irrespective of the formulation or brand. It may be administered as single entity products given concurrently or as a finished pharmaceutical product.

**Generic Pharmaceutical Product** is a pharmaceutically equivalent product that may or may not be therapeutically equivalent or bioequivalent. Generic pharmaceutical products that are therapeutically equivalent are interchangeable.

**High solubility:** A Pharmaceutical product is classified as highly soluble if the highest therapeutic dose of the Pharmaceutical product is completely soluble in 250 mL or less of solvent over the pH range of 1.2-6.8 at 37 ± 1°C, that is (i.e.), DSV ≤ 250 mL over the pH range.

**Highest dose** - highest approved therapeutic dose for the Pharmaceutical product in EAC. If not currently approved in EAC, the highest proposed dose is applicable.

**Low absorption:** less than (<) 85% of the administered dose absorbed.

**Low solubility:** A Pharmaceutical product is classified as a low solubility compound if the highest therapeutic dose of the Pharmaceutical product is not completely

soluble in 250 mL of solvent at any pH within the pH range of 1.2-6.8 at 37 ± 1°C, i.e., DSV greater than (>) 250 mL at any pH within the range.

**Pharmaceutical alternatives:** Pharmaceutical products are pharmaceutical alternatives if they contain the same active moiety but differ either in chemical form (e.g. salt, ester) of that moiety or in the dosage form or strength, administered by the same route of administration but are otherwise not pharmaceutically equivalent. Pharmaceutical alternatives do not necessarily imply bioequivalence.

**Pharmaceutical Dosage Form:** A pharmaceutical dosage form is the form of the completed pharmaceutical product e.g. tablet, capsule, injection, elixir, suppository.

**Pharmaceutical Equivalence:** Pharmaceutical products are pharmaceutically equivalent if they contain the same amount of the same API(s) in the same dosage form, if they meet the same or comparable standards and if they are intended to be administered by the same route. Pharmaceutical equivalence does not necessarily imply bioequivalence as differences in the excipients and/or the manufacturing process can lead to changes in dissolution and/or absorption.

**Pharmaceutical Product:** Any preparation for human (or animal) use, containing one or more APIs with or without pharmaceutical excipients or additives, that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

**Proportionally Similar Dosage Forms/Products:** Pharmaceutical products are considered proportionally similar in the following cases:-

**Rapidly dissolving product** - a product in which not less than 85% of the labelled amount is released within 30 minutes or less during a product dissolution test under the conditions specified in these guidelines.

**Solution** - a homogenous mixture in a single phase with no precipitate.

**Therapeutic Equivalence:** Two pharmaceutical products are therapeutically equivalent if they are pharmaceutically equivalent or are pharmaceutical alternatives and, after administration in the same molar dose, their effects with respect to both efficacy and safety are essentially the same, as determined from appropriate bioequivalence, pharmacodynamic, clinical or *in vitro* studies.

**Very rapidly dissolving product** - not less than 85% of the labelled amount is released within 15 minutes or less during a product dissolution test under the conditions specified in this guidelines.

## 1.0 INTRODUCTION

The objective of this guideline is to specify the requirements for the design, conduct, and evaluation of bioequivalence studies for immediate release and modified release dosage forms with systemic action.

Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or Pharmaceutical alternatives and their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable *in vivo* performance, i.e. similarity in terms of safety and efficacy.

In bioequivalence studies, the plasma concentration time curve is generally used to assess the rate and extent of absorption. Selected pharmacokinetic parameters and pre-set acceptance limits allow the final decision on bioequivalence of the tested products. The absorption rate of a drug is influenced by pharmacokinetic parameters like AUC, the area under the concentration time curve, reflects the extent of exposure, $C_{max}$, the maximum plasma concentration or peak exposure, and the time to maximum plasma concentration, $t_{max}$. In applications for generic medicinal products to EAC, the concept of bioequivalence is fundamental.

The purpose of establishing bioequivalence is to demonstrate equivalence in biopharmaceutics quality between the generic medicinal product and a comparator medicinal product in order to allow bridging of preclinical tests and of clinical trials associated with the comparator medicinal product. The definition for generic medicinal products is a product that has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the comparator medicinal product, and whose bioequivalence with the comparator medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. Furthermore, the various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form. Other types of applications may also require demonstration of bioequivalence, including variations, fixed combinations, extensions and hybrid applications.

The recommendations on design and conduct given for bioequivalence studies in this guideline may also be applied to comparative bioavailability studies evaluating different formulations used during the development of a new medicinal product containing a new chemical entity and to comparative bioavailability studies included in extension or hybrid applications that are not based exclusively on bioequivalence data.

Generally, results from comparative bioavailability studies should be provided in support of the safety and efficacy of each proposed product and of each proposed strength included in the submission. In the absence of such studies, a justification supporting a waiver of this requirement should be provided in this section for each product and each strength. For example, if there are several strengths of the proposed product, and comparative bioavailability data has not been submitted for all strengths, the applicant should provide a scientific justification for not conducting studies on each strength. This justification may address issues such as the nature of the kinetics of the drug (e.g., linear versus non-linear), and the proportionality of the strengths for which a waiver is sought to the strength on which a comparative bioavailability study was conducted.

The statement of justification for waiver will include supporting data (e.g. comparative dissolution data) which should be provided in the relevant module(s) of the CTD submission (i.e., Modules 2-5). For example, comparative dissolution profiles should be provided in Module 3, Section 3.2.P.2 of the main EAC Guidelines on Documentation for Application of Human Pharmaceutical Products (Pharmaceutical Development).

## 2.0 SCOPE

This guideline focuses on recommendations for bioequivalence studies for immediate release formulations and modified release with systemic action. The scope is limited to chemical entities. Biological products are not covered by these guidelines.

In case bioequivalence cannot be demonstrated using drug concentrations, in exceptional circumstances pharmacodynamic or clinical endpoints may be needed.

### Exemptions for carrying out bioequivalence studies

Omission of BE studies must be justified except if a product fulfils one or more of the following conditions:-

a) Solutions, complex or simple, which do not contain any ingredient which can be regarded as a pharmacologically active substance;

b) Simple aqueous solutions intended for intravenous injection or infusion containing the same active substance(s) in the same concentration as innovator products. Simple solutions do not include complex solution such as micellar or liposomal solutions;

c) Solutions for injection that contain the same active ingredients and excipients in the same concentrations as innovator products and which are administered by the same route(s);

d) Products that are powder for reconstitution as a solution and the solution meets either criterion (c) or (d) above;

e) Oral immediate release tablets, capsules and suspensions containing active pharmaceutical ingredients with high solubility and high permeability and where the pharmaceutical product has a high dissolution rate, provided the applicant submits an acceptable justification for not providing bioequivalence data;

f) Oral solutions containing the same active ingredient(s) in the same concentration as a currently registered oral solution and not containing excipients that may significantly affect gastric passage or absorption of the active ingredient(s);

g) Products for topical use provided the product is intended to act without systemic absorption when applied locally;

h) Products containing therapeutic substances, which are not systemically or locally absorbed i.e. an oral dosage form, which is not intended to be absorbed (e.g., barium sulphate enemas, Antacid, Radioopaque Contrast Media, or powders in which no ingredient is absorbed etc.). If there is doubt as to whether absorption occurs, a study or justification may be required;

i) Otic or ophthalmic products prepared as aqueous solutions and containing the same active pharmaceutical ingredient(s) in the same concentration;

j) The product is a solution intended solely for intravenous administration;

k) The product is to be parenterally or orally administered as a solution;

l) The product is an oral solution, syrup, or other similarly solubilized form;

m) The product is oro-dispersable product is eligible for a biowaiver application only if there is no buccal or sublingual absorption and the product is labelled to be consumed with water;

n) The product is a solution intended for ophthalmic or otic administration;

o) The product is an inhalant volatile anaesthetic solution, Inhalation and nasal preparations;

p) The product is a reformulated product by the original manufacturer that is identical to the original product except for colouring agents, flavouring agents or preservatives, which are recognized as having no influence upon bioavailability;

q) Gases;

r) Solutions for oral use which contain the active substance(s) in the same concentration as the innovator product and do not contain an excipient that affects gastro-intestinal transit or absorption of the active substance;

s) Powders for reconstitution as a solution and the solution meets the criteria indicated in (k) above.

## 3.0 MAIN GUIDELINES TEXT

### 3.1 Design, conduct and evaluation of bioequivalence studies

The design, conduct and evaluation of the Bioequivalence study should comply with ICH GCP requirements (E6).

In the following sections, requirements for the design and conduct of comparative bioavailability studies are formulated. Investigator(s) should have appropriate expertise, qualifications and competence to undertake a proposed study and is familiar with pharmacokinetic theories underlying bioavailability studies. The design should be based on a reasonable knowledge of the pharmacodynamics and/or the pharmacokinetics of the active substance in question.

The number of studies and study design depend on the physico-chemical characteristics of the substance, its pharmacokinetic properties and proportionality in composition, and should be justified accordingly. In particular it may be necessary to address the linearity of pharmacokinetics, the need for studies both in fed and fasting state, the need for enantioselective analysis and the possibility of waiver for additional strengths (see Sections 3.1.4, 3.1.5 and 3.1.6).

Module 2.7.1 should list all relevant studies carried out with the product applied for, i.e. bioequivalence studies comparing the formulation applied for (i.e. same composition and manufacturing process) with a Comparator medicinal product. Studies should be included in the list regardless of the study outcome. Full study reports should be provided for all studies, except pilot studies for which study report synopses (in accordance with ICH E3) are sufficient. Full study reports for pilot studies should be available upon request. Study report synopses for bioequivalence or comparative bioavailability studies conducted during formulation development should also be included in Module 2.7. Bioequivalence studies comparing the product applied for with non-WHO Comparator products should not be submitted and do not need to be included in the list of studies.

#### 3.1.1 Study design

**Standard design**

If two formulations are compared, a randomized, two-period, two-sequence single

dose crossover design is recommended. The treatment periods should be separated by a wash out period sufficient to ensure that drug concentrations are below the lower limit of bioanalytical quantification in all subjects at the beginning of the second period. Normally at least 5 elimination half-lives are necessary to achieve this. The study should be designed in such a way that the treatment effect (formulation effect) can be distinguished from other effects. In order to reduce variability a cross over design usually is the first choice.

**Alternative designs**

Under certain circumstances, provided the study design and the statistical analyses are scientifically sound, alternative well-established designs could be considered such as parallel design for substances with very long half -life and replicate designs e.g. for substances with highly variable pharmacokinetic characteristics (see Section 3.1.10). The study should be designed in such a way that the formulation effect can be distinguished from other effects.

Other designs or methods may be chosen in specific situations, but should be fully justified in the protocol and final study report. The subjects should be allocated to treatment sequences in a randomized order. In general, single dose studies will suffice, but there are situations in which steady-state studies may be required:-

(a) If problems of sensitivity preclude sufficiently precise plasma concentration measurement after single dose;

(b) If the intra-individual variability in the plasma concentrations or disposition rate is inherently large;

(c) in the case of dose-or time-dependent pharmacokinetics;

(d) in the case of extended release products (in addition to single dose studies)

In such steady-state studies, the administration scheme should follow the usual dosage recommendations.

Conduct of a multiple dose study in patients is acceptable if a single dose study cannot be conducted in healthy volunteers due to tolerability reasons, and a single dose study is not feasible in patients.

In the rare situation where problems of sensitivity of the analytical method preclude sufficiently precise plasma concentration measurements after single dose administration and where the concentrations at steady state are sufficiently high to be reliably measured, a multiple dose study may be acceptable as an alternative to the single dose study. However, given that a multiple dose study is less sensitive in detecting differences in $C_{max}$, this will only be acceptable if the applicant can

adequately justify that the sensitivity of the analytical method cannot be improved and that it is not possible to reliably measure the parent compound after single dose administration taking into account also the option of using a supra-therapeutic dose in the bioequivalence study (see also Section 3.1.6). Due to the recent development in the bioanalytical methodology, it is unusual that parent drug cannot be measured accurately and precisely. Hence, use of a multiple dose study instead of a single dose study, due to limited sensitivity of the analytical method, will only be accepted in exceptional cases.

In steady-state studies, the washout period of the previous treatment can overlap with the build-up of the second treatment, provided the build-up period is sufficiently long (at least 5 times the terminal half-life).

### 3.1.2 Comparator and test products

**Comparator Product**

Test products in an application for a generic or hybrid product or an extension of a generic/hybrid product are normally compared with the corresponding dosage form of a comparator medicinal product, if available on the market. The product used as comparator product in the bioequivalence study should meet the criteria stipulated in **Annex V**.

In an application for extension of a medicinal product which has been initially approved by EAC and when there are several dosage forms of this medicinal product on the market, it is recommended that the dosage form used for the initial approval of the concerned medicinal product (and which was used in clinical efficacy and safety studies) is used as comparator product, if available on the market.

The selection of the Comparator product used in a bioequivalence study should be based on assay content and dissolution data and is the responsibility of the Applicant. Unless otherwise justified, the assayed content of the batch used as test product should not differ more than 5% from that of the batch used as comparator product determined with the test procedure proposed for routine quality testing of the test product. The Applicant should document how a representative batch of the comparator product with regards to dissolution and assay content has been selected. It is advisable to investigate more than one single batch of the Comparator product when selecting Comparator product batch for the bioequivalence study.

**Test product**

The test product used in the study should be representative of the product to be marketed and this should be discussed and justified by the applicant. For example, for oral solid forms for systemic action:-

a) The test product should usually originate from a batch of at least 1/10 of production scale or 100,000 units, whichever is greater, unless otherwise justified.

b) The production of batches used should provide a high level of assurance that the product and process will be feasible on an industrial scale.

   In case of a production batch smaller than 100,000 units, a full production batch will be required.

c) The characterization and specification of critical quality attributes of the finished pharmaceutical product, such as dissolution, should be established from the test batch, i.e. the clinical batch for which bioequivalence has been demonstrated.
d) Samples of the product from additional pilot and/or full scale production batches, submitted to support the application, should be compared with those of the bioequivalence study test batch, and should show similar in vitro dissolution profiles when employing suitable dissolution test conditions.
e) Comparative dissolution profile testing should be undertaken on the first three production batches.
f) If full-scale production batches are not available at the time of submission, the applicant should not market a batch until comparative dissolution profile testing has been completed.
g) The results should be provided at a Competent Authority's request or if the dissolution profiles are not similar together with proposed action to be taken.

For other immediate release pharmaceutical forms for systemic action, justification of the representative nature of the test batch should be similarly established.

**Impact of excipients**

Identify any excipients present in either product that are known to impact on *in vivo* absorption processes. Provide a literature-based summary of the mechanism by which these effects are known to occur should be included and relevant full discussion enclosed, if applicable.

**Comparative qualitative and quantitative differences between the compositions of the test and comparator products**

Identify all qualitative (and quantitative, if available) differences between the compositions of the test and comparator products. The data obtained and methods used for the determination of the quantitative composition of the comparator product as required by the guidance documents should be summarized here for assessment.

**Impact of the differences between the compositions of the test and comparator products**

Provide a detailed comment on the impact of any differences between the compositions of the test and comparator products with respect to drug release and in vivo absorption

**Packaging of study products**

The comparator and test products should be packed in an individual way for each subject and period, either before their shipment to the trial site, or at the trial site itself. Packaging (including labelling) should be performed in accordance with good manufacturing practice.

It should be possible to identify unequivocally the identity of the product administered to each subject at each trial period. Packaging, labelling and administration of the products to the subjects should therefore be documented in detail. This documentation should include all precautions taken to avoid and identify potential dosing mistakes. The use of labels with a tear-off portion is recommended.

### 3.1.3 Subjects

**Number of subjects**

The number of subjects to be included in the study should be based on an appropriate sample size calculation. The number of evaluable subjects in a bioequivalence study should not be less than 12.

In general, the recommended number of 24 normal healthy subjects, preferably non-smoking. A number of subjects of less than 24 may be accepted (with a minimum of 12 subjects) when statistically justifiable. However, in some cases (e.g. for highly variable drugs) more than 24 subjects are required for acceptable bioequivalence study. The number of subjects should be determined using appropriate methods taking into account the error variance associated with the primary parameters to be studied (as estimated for a pilot experiment, from previous studies or from published data), the significance level desired and the deviation from the comparator product compatible with bioequivalence (± 20%) and compatible with safety and efficacy. For a parallel design study a greater number of subjects may be required to achieve sufficient study power.

Applicants should enter a sufficient number of subjects in the study to allow for dropouts. Because replacement of subjects could complicate the statistical model and analysis, dropouts generally should not be replaced.

**Selection of subjects**

The subject population for bioequivalence studies should be selected with the aim of permitting detection of differences between pharmaceutical products. The subject population for bioequivalence studies should be selected with the aim to minimise variability and permit detection of differences between pharmaceutical products. In order to reduce variability not related to differences between products, the studies should normally be performed in healthy volunteers unless the drug carries safety concerns that make this unethical. This model, *in vivo* healthy volunteers, is regarded as adequate in most instances to detect formulation differences and to allow extrapolation of the results to populations for which the comparator medicinal product is approved (the elderly, children, patients with renal or liver impairment, etc.).

The inclusion/exclusion criteria should be clearly stated in the protocol. Subjects should be 1 between18-50years in age, preferably have a Body Mass Index between 18.5 and 30 $kg/m^2$ and within15% of ideal body weight, height and body build to be enrolled in a crossover bioequivalence study.

The subjects should be screened for suitability by means of clinical laboratory tests, a medical history, and a physical examination. Depending on the drug's therapeutic class and safety profile, special medical investigations and precautions may have to be carried out before, during and after the completion of the study.

Subjects could belong to either sex; however, the risk to women of childbearing potential should be considered. Subjects should preferably be non -smokers and without a history of alcohol or drug abuse. Phenotyping and/or genotyping of subjects may be considered for safety or pharmacokinetic reasons.

In parallel design studies, the treatment groups should be comparable in all known variables that may affect the pharmacokinetics of the active substance (e.g. age, body weight, sex, ethnic origin, smoking status, extensive/poor metabolic status). This is an essential pre-requisite to give validity to the results from such studies.

**Inclusion of patients**

If the investigated active substance is known to have adverse effects and the pharmacological effects or risks are considered unacceptable for healthy volunteers, it may be necessary to include patients instead, under suitable precautions and supervision. In this case the applicant should justify the alternative.

### 3.1.4 Study conduct

**Standardisation of the bioequivalence studies**

The test conditions should be standardized in order to minimize the variability of all factors involved except that of the products being tested. Therefore, it is recommended to standardize diet, fluid intake and exercise.

The time of day for ingestion should be specified. Subjects should fast for at least 8 hours prior to administration of the products, unless otherwise justified. As fluid intake may influence gastric passage for oral administration forms, the test and comparator products should be administered with a standardized volume of fluid (at least 150 ml). It is recommended that water is allowed as desired except for one hour before and one hour after drug administration and no food is allowed for at least 4 hours post-dose. Meals taken after dosing should be standardized in regard to composition and time of administration during an adequate period of time (e.g. 12 hours).

In case the study is to be performed during fed conditions, the timing of administration of the finished pharmaceutical product in relation to food intake is recommended to be according to the SmPC of the originator product. If no specific recommendation is given in the originator SmPC, it is recommended that subjects should start the meal 30 minutes prior to administration of the finished pharmaceutical product and eat this meal within 30 minutes.

As the bioavailability of an active moiety from a dosage form could be dependent upon gastrointestinal transit times and regional blood flows, posture and physical activity may need to be standardized.

The subjects should abstain from food and drinks, which may interact with circulatory, gastrointestinal, hepatic or renal function (e.g. alcoholic drinks or certain fruit juices such as grapefruit juice) during a suitable period before and during the study. Subjects should not take any other concomitant medication (including herbal remedies) for an appropriate interval before as well as during the study. Contraceptives are, however, allowed. In case concomitant medication is unavoidable and a subject is administered other drugs, for instance to treat adverse events like headache, the use must be reported (dose and time of administration) and possible effects on the study outcome must be addressed. In rare cases, the use of a concomitant medication is needed for all subjects for safety or tolerability reasons (e.g. opioid antagonists, anti -emetics). In that scenario, the risk for a potential interaction or bioanalytical interference affecting the results must be addressed.

Medicinal products that according to the originator SmPC are to be used explicitly in combination with another product (e.g. certain protease inhibitors in combination with ritonavir) may be studied either as the approved combination or without the product recommended to be administered concomitantly.

In bioequivalence studies of endogenous substances, factors that may influence the endogenous baseline levels should be controlled if possible (e.g. strict control of

dietary intake).

**Sampling times**

Several samples of appropriate biological matrix (blood, plasma/serum, urine) are collected at various time intervals post-dose. The sampling schedule depends on the pharmacokinetic characteristics of the drug being tested. In most cases, plasma or serum is the matrix of choice. However, if the parent drug is not metabolized and is largely excreted unchanged and can be suitably assayed in the urine, urinary drug levels may be used to assess bioequivalence, if plasma/serum concentrations of the drug cannot be reliably measured.

A sufficient number of samples are collected during the absorption phase to adequately describe the plasma concentration-time profile should be collected. The sampling schedule should include frequent sampling around predicted $T_{max}$ to provide a reliable estimate of peak exposure. Intensive sampling is carried out around the time of the expected peak concentration. In particular, the sampling schedule should be planned to avoid $C_{max}$ being the first point of a concentration time curve. The sampling schedule should also cover the plasma concentration time curve long enough to provide a reliable estimate of the extent of exposure which is achieved if $AUC_{(0-t)}$ covers at least 80% of $AUC_{(0-\infty)}$. At least three to four samples are needed during the terminal log-linear phase in order to reliably estimate the terminal rate constant (which is needed for a reliable estimate of $AUC_{(0-\infty)}$. AUC truncated at 72 h [$AUC_{(0-72h)}$] may be used as an alternative to $AUC_{(0-t)}$ for comparison of extent of exposure as the absorption phase has been covered by 72 h for immediate release formulations. A sampling period longer than 72 h is therefore not considered necessary for any immediate release formulation irrespective of the half-life of the drug. Sufficient numbers of samples should also be collected in the log-linear elimination phase of the drug so that the terminal elimination rate constant and half-life of the drug can be accurately determined. A sampling period extending to at least five terminal elimination half-lives of the drug or five the longest half-life of the pertinent analyte (if more than one analyte) is usually sufficient. The samples are appropriately processed and stored carefully under conditions that preserve the integrity of the analyte(s).

In multiple -dose studies, the pre-dose sample should be taken immediately before (within 5 minutes) dosing and the last sample is recommended to be taken within 10 minutes of the nominal time for the dosage interval to ensure an accurate determination of $AUC_{(0-\tau)}$.

If urine is used as the biological sampling fluid, urine should normally be collected over no less than three times the terminal elimination half-life. However, in line with the recommendations on plasma sampling, urine does not need to be collected for more than 72 h. If rate of excretion is to be determined, the collection intervals need to be as short as feasible during the absorption phase (see also Section 3.1.5).

For endogenous substances, the sampling schedule should allow characterization of the endogenous baseline profile for each subject in each period. Often, a baseline is determined from 2-3 samples taken before the finished pharmaceutical products are administered. In other cases, sampling at regular intervals throughout 1-2 day(s) prior to administration may be necessary in order to account for fluctuations in the endogenous baseline due to circadian rhythms (see Section 3.1.5).

**Washout period**

Subsequent treatments should be separated by periods long enough to eliminate the previous dose before the next one (wash-out period). In steady-state studies wash-out of the last dose of the previous treatment can overlap with the build-up of the second treatment, provided the build-up period is sufficiently long (at least five (5) times the dominating half-life).

**Fasting or fed conditions**

In general, a bioequivalence study should be conducted under fasting conditions as this is considered to be the most sensitive condition to detect a potential difference between formulations. For products where the SmPC recommends intake of the innovator medicinal product on an empty stomach or irrespective of food intake, the bioequivalence study should hence be conducted under fasting conditions. For products where the SmPC recommends intake of the innovator medicinal product only in fed state, the bioequivalence study should generally be conducted under fed conditions.

However, for products with specific formulation characteristics (e.g. microemulsions, prolonged modified release, solid dispersions), bioequivalence studies performed under both fasted and fed conditions are required unless the product must be taken only in the fasted state or only in the fed state.

In cases where information is required in both the fed and fasted states, it is acceptable to conduct either two separate two-way cross-over studies or a four-way cross-over study.

In studies performed under fed conditions, the composition of the meal is recommended to be according to the SmPC of the originator product. If no specific recommendation is given in the originator SmPC, the meal should be a high-fat (approximately 50 percent of total caloric content of the meal) and high -calorie (approximately 800 to 1000 kcal) meal. This test meal should derive approximately 150, 250, and 500-600 kcal from protein, carbohydrate, and fat, respectively. The composition of the meal should be described with regard to protein, carbohydrate and fat content (specified in grams, calories and relative caloric content (%).

### 3.1.5 Characteristics to be investigated

**Pharmacokinetic parameters (Bioavailability Metrics)**

Actual time of sampling should be used in the estimation of the pharmacokinetic parameters. In studies to determine bioequivalence after a single dose, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, residual area, $C_{max}$ and $t_{max}$ should be determined. In studies with a sampling period of 72 h, and where the concentration at 72 h is quantifiable, $AUC_{(0-\infty)}$ and residual area do not need to be reported; it is sufficient to report AUC truncated at 72h, $AUC_{(0-72h)}$. Additional parameters that may be reported include the terminal rate constant, $\lambda z$, and $t_{1/2}$.

In studies to determine bioequivalence for immediate release formulations at steady state, $AUC_{(0-\tau)}$, $C_{max,ss}$, and $t_{max,ss}$ should be determined.

When using urinary data, $Ae_{(0-t)}$ and, if applicable, $R_{max}$ should be determined.

Non-compartmental methods should be used for determination of pharmacokinetic parameters in bioequivalence studies. The use of compartmental methods for the estimation of parameters is not acceptable.

**Parent compound or metabolites**

In principle, evaluation of bioequivalence should be based upon measured concentrations of the parent compound. The reason for this is that $C_{max}$ of a parent compound is usually more sensitive to detect differences between formulations in absorption rate than $C_{max}$ of a metabolite.

**Inactive pro-drugs**

Also for inactive pro-drugs, demonstration of bioequivalence for parent compound is recommended. The active metabolite does not need to be measured. However, some pro-drugs may have low plasma concentrations and be quickly eliminated resulting in difficulties in demonstrating bioequivalence for parent compound. In this situation it is acceptable to demonstrate bioequivalence for the main active metabolite without measurement of parent compound. In the context of this guideline, a parent compound can be considered to be an inactive pro-drug if it has no or very low contribution to clinical efficacy.

**Use of metabolite data as surrogate for active parent compound**

The use of a metabolite as a surrogate for an active parent compound is not encouraged. This can only be considered if the applicant can adequately justify that the sensitivity of the analytical method for measurement of the parent compound cannot be improved and that it is not possible to reliably measure the parent

compound after single dose administration taking into account also the option of using a higher single dose in the bioequivalence study. Due to recent developments in bioanalytical methodology it is unusual that parent drug cannot be measured accurately and precisely. Hence, the use of a metabolite as a surrogate for active parent compound is expected to be accepted only in exceptional cases. When using metabolite data as a substitute for active parent drug concentrations, the applicant should present any available data supporting the view that the metabolite exposure will reflect parent drug and that the metabolite formation is not saturated at therapeutic doses.

**Enantiomers**

The use of achiral bioanalytical methods is generally acceptable. However, the individual enantiomers should be measured when all the following conditions are met:-

a) the enantiomers exhibit different pharmacokinetics;

b) the enantiomers exhibit pronounced difference in pharmacodynamics;

c) the exposure (AUC) ratio of enantiomers is modified by a difference in the rate of absorption.

The individual enantiomers should also be measured if the above conditions are fulfilled or are unknown. If one enantiomer is pharmacologically active and the other is inactive or has a low contribution to activity, it is sufficient to demonstrate bioequivalence for the active enantiomer.

**The use of urinary data**

If drug/API concentrations in blood are too low to be detected and a substantial amount (> 40 %) of the drug/API is eliminated unchanged in the urine, then urine may serve as the biological fluid to be sampled.

If a reliable plasma $C_{max}$ can be determined, this should be combined with urinary data on the extent of exposure for assessing bioequivalence. When using urinary data, the applicant should present any available data supporting that urinary excretion will reflect plasma exposure.

When urine is collected:-

a) The volume of each sample should be measured immediately after collection and included in the report.

b) Urine should be collected over an extended period and generally no less than

seven times the terminal elimination half-life, so that the amount excreted to infinity ($Ae_\infty$) can be estimated.

c) Sufficient samples should be obtained to permit an estimate of the rate and extent of renal excretion. For a 24-hour study, sampling times of 0 to 2, 2 to 4, 4 to 8, 8 to 12, and 12 to 24 hours post-dose are usually appropriate.

d) The actual clock time when samples are collected, as well as the elapsed time relative to API administration, should be recorded.

Urinary Excretion Profiles:-

In the case of API's predominantly excreted renally, the use of urine excretion data may be advantageous in determining the extent of drug/API input. However, justification should also be given when this data is used to estimate the rate of absorption.

Sampling points should be chosen so that the cumulative urinary excretion profiles can be defined adequately so as to allow accurate estimation of relevant parameters.

The following bioavailability parameters are to be estimated:-

a) $Ae_t$, $Ae_\infty$ as appropriate for urinary excretion studies.

b) Any other justifiable characteristics.

c) The method of estimating AUC-values should be specified.

**Endogenous substances**

If the substance being studied is endogenous, the calculation of pharmacokinetic parameters should be performed using baseline correction so that the calculated pharmacokinetic parameters refer to the additional concentrations provided by the treatment. Administration of supra -therapeutic doses can be considered in bioequivalence studies of endogenous drugs, provided that the dose is well tolerated, so that the additional concentrations over baseline provided by the treatment may be reliably determined. If a separation in exposure following administration of different doses of a particular endogenous substance has not been previously established this should be demonstrated, either in a pilot study or as part of the pivotal bioequivalence study using different doses of the comparator formulation, in order to ensure that the dose used for the bioequivalence comparison is sensitive to detect potential differences between formulations.

The exact method for baseline correction should be pre-specified and justified in the study protocol. In general, the standard subtractive baseline correction method, meaning either subtraction of the mean of individual endogenous pre-dose

concentrations or subtraction of the individual endogenous pre-dose AUC, is preferred. In rare cases where substantial increases over baseline endogenous levels are seen, baseline correction may not be needed.

In bioequivalence studies with endogenous substances, it cannot be directly assessed whether carry-over has occurred, so extra care should be taken to ensure that the washout period is of an adequate duration.

### 3.1.6 Strength to be investigated

If several strengths of a test product are applied for, it may be sufficient to establish bioequivalence at only one or two strengths, depending on the proportionality in composition between the different strengths and other product related issues described below. The strength(s) to evaluate depends on the linearity in pharmacokinetics of the active substance.

In case of non-linear pharmacokinetics (i.e. not proportional increase in AUC with increased dose) there may be a difference between different strengths in the sensitivity to detect potential differences between formulations. In the context of this guideline, pharmacokinetics is considered to be linear if the difference in dose-adjusted mean AUCs is no more than 25% when comparing the studied strength (or strength in the planned bioequivalence study) and the strength(s) for which a waiver is considered. In order to assess linearity, the applicant should consider all data available in the public domain with regard to the dose proportionality and review the data critically. Assessment of linearity will consider whether differences in dose-adjusted AUC meet a criterion of ± 25%.

If bioequivalence has been demonstrated at the strength(s) that are most sensitive to detect a potential difference between products, in vivo bioequivalence studies for the other strength(s) can be waived.

**General biowaiver criteria**

The following general requirements must be met where a waiver for additional strength(s) is claimed:-

a) the pharmaceutical products are manufactured by the same manufacturing process,

b) the qualitative composition of the different strengths is the same,

c) the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),

If there is some deviation from quantitatively proportional composition, condition c is still considered fulfilled if condition i) and ii) or i) and iii) below apply to the strength used in the bioequivalence study and the strength(s) for which a waiver is considered:-

i. the amount of the active substance(s) is less than 5 % of the tablet core weight, the weight of the capsule content.

ii. the amounts of the different core excipients or capsule content are the same for the concerned strengths and only the amount of active substance is changed.

iii. the amount of a filler is changed to account for the change in amount of active substance. The amounts of other core excipients or capsule content should be the same for the concerned strengths.

d) An appropriate in vitro dissolution data should confirm the adequacy of waiving additional in vivo bioequivalence testing (see Section 3.2).

**Linear pharmacokinetics**

For products where all the above conditions a) to d) are fulfilled, it is sufficient to establish bioequivalence with only one strength.

The bioequivalence study should in general be conducted at the highest strength. For products with linear pharmacokinetics and where the active pharmaceutical ingredient is highly soluble, selection of a lower strength than the highest is also acceptable. Selection of a lower strength may also be justified if the highest strength cannot be administered to healthy volunteers for safety/tolerability reasons. Further, if problems of sensitivity of the analytical method preclude sufficiently precise plasma concentration measurements after single dose administration of the highest strength, a higher dose may be selected (preferably using multiple tablets of the highest strength). The selected dose may be higher than the highest therapeutic dose provided that this single dose is well tolerated in healthy volunteers and that there are no absorption or solubility limitations at this dose.

**Non-linear pharmacokinetics**

For drugs with non-linear pharmacokinetics characterized by a more than proportional increase in AUC with increasing dose over the therapeutic dose range, the bioequivalence study should in general be conducted at the highest strength. As for drugs with linear pharmacokinetics a lower strength may be justified if the highest strength cannot be administered to healthy volunteers for safety/tolerability reasons. Likewise a higher dose may be used in case of sensitivity problems of the analytical method in line with the recommendations given for products with linear pharmacokinetics above.

For drugs with a less than proportional increase in AUC with increasing dose over the therapeutic dose range, bioequivalence should in most cases be established both at the highest strength and at the lowest strength (or strength in the linear range), i.e. in this situation two bioequivalence studies are needed. If the non-linearity is not caused by limited solubility but is due to e.g. saturation of uptake transporters and provided that conditions a) to d) above are fulfilled and the test and comparator products do not contain any excipients that may affect gastrointestinal motility or transport proteins, it is sufficient to demonstrate bioequivalence at the lowest strength (or a strength in the linear range).

Selection of other strengths may be justified if there are analytical sensitivity problems preventing a study at the lowest strength or if the highest strength cannot be administered to healthy volunteers for safety/tolerability reasons.

**Bracketing approach**

Where bioequivalence assessment at more than two strengths is needed, e.g. because of deviation from proportional composition, a bracketing approach may be used. In this situation it can be acceptable to conduct two bioequivalence studies, if the strengths selected represent the extremes, e.g. the highest and the lowest strength or the two strengths differing most in composition, so that any differences in composition in the remaining strengths is covered by the two conducted studies.

Where bioequivalence assessment is needed both in fasting and in fed state and at two strengths due to nonlinear absorption or deviation from proportional composition, it may be sufficient to assess bioequivalence in both fasting and fed state at only one of the strengths. Waiver of either the fasting or the fed study at the other strength(s) may be justified based on previous knowledge and/or pharmacokinetic data from the study conducted at the strength tested in both fasted and fed state. The condition selected (fasting or fed) to test the other strength(s) should be the one which is most sensitive to detect a difference between products.

**Fixed combinations**

The conditions regarding proportional composition should be fulfilled for all active substances of fixed combinations. When considering the amount of each active substance in a fixed combination the other active substance(s) can be considered as excipients. In the case of bilayer tablets, each layer may be considered independently.

### 3.1.7 Bioanalytical methodology

The bioanalysis of bioequivalence samples should be performed in accordance with the principles of Good Laboratory Practice (GLP). However, as human bioanalytical studies fall outside the scope of GLP, the sites conducting the studies are not required to be monitored as part of a national GLP compliance programme.

The bioanalytical methods used to determine the active principle and/or its biotransformation products in plasma, serum, blood or urine or any other suitable matrix must be well characterized, fully validated and documented to yield reliable results that can be satisfactorily interpreted. Within study validation should be performed using Quality control samples in each analytical run.

The main objective of method validation is to demonstrate the reliability of a particular method for the quantitative determination of analyte(s) concentration in a specific biological matrix. The main characteristics of a bioanalytical method that is essential to ensure the acceptability of the performance and the reliability of analytical results includes but not limited to: selectivity, sensitivity, lower limit of quantitation, the response function (calibration curve performance), accuracy, precision and stability of the analyte(s) in the biological matrix under processing conditions and during the entire period of storage.

The lower limit of quantitation should be 1/20 of $C_{max}$ or lower, as pre-dose concentrations should be detectable at 5% of $C_{max}$ or lower (see Section 3.1.8 *Carry-over effects*).

Reanalysis of study samples should be predefined in the study protocol (and/or SOP) before the actual start of the analysis of the samples. Normally reanalysis of subject samples because of a pharmacokinetic reason is not acceptable. This is especially important for bioequivalence studies, as this may bias the outcome of such a study.

Analysis of samples should be conducted without information on treatment.

The validation report of the bioanalytical method should be included in Module 5 of the application.

### 3.1.8 Evaluation

In bioequivalence studies, the pharmacokinetic parameters should in general not be adjusted for differences in assayed content of the test and comparator batch. However, in exceptional cases where a comparator batch with an assay content differing less than 5% from test product cannot be found (see Section 3.1.2 on Comparator and test product) content correction could be accepted. If content correction is to be used, this should be pre-specified in the protocol and justified by inclusion of the results from the assay of the test and comparator products in the protocol.

**Subject accountability**

Ideally, all treated subjects should be included in the statistical analysis. However, subjects in a crossover trial who do not provide evaluable data for both of the test and comparator products (or who fail to provide evaluable data for the single period in a parallel group trial) should not be included.

The data from all treated subjects should be treated equally. It is not acceptable to have a protocol, which specifies that 'spare' subjects will be included in the analysis only if needed as replacements for other subjects who have been excluded. It should be planned that all treated subjects should be included in the analysis, even if there are no drop-outs.
In studies with more than two treatment arms (e.g. a three period study including two comparators, one from EU and another from USA, or a four period study including test and comparator in fed and fasted states), the analysis for each comparison should be conducted excluding the data from the treatments that are not relevant for the comparison in question.

**Reasons for exclusion**

Unbiased assessment of results from randomized studies requires that all subjects are observed and treated according to the same rules. These rules should be independent from treatment or outcome. In consequence, the decision to exclude a subject from the statistical analysis must be made before bioanalysis.

In principle any reason for exclusion is valid provided it is specified in the protocol and the decision to exclude is made before bioanalysis. However the exclusion of data should be avoided, as the power of the study will be reduced and a minimum of 12 evaluable subjects is required.

Examples of reasons to exclude the results from a subject in a particular period are events such as vomiting and diarrhoea, which could render the plasma concentration-time profile unreliable. In exceptional cases, the use of concomitant medication could be a reason for excluding a subject.

The permitted reasons for exclusion must be pre-specified in the protocol. If one of these events occurs it should be noted in the CRF as the study is being conducted. Exclusion of subjects based on these pre-specified criteria should be clearly described and listed in the study report.

Exclusion of data cannot be accepted on the basis of statistical analysis or for pharmacokinetic reasons alone, because it is impossible to distinguish the formulation effects from other effects influencing the pharmacokinetics.
The exceptions to this are:-

1) A subject with lack of any measurable concentrations or only very low plasma concentrations for comparator medicinal product. A subject is considered to have very low plasma concentrations if its AUC is less than 5% of comparator medicinal product geometric mean AUC (which should be calculated without inclusion of data from the outlying subject). The exclusion of data due to this reason will only be accepted in exceptional cases and may question the validity of the trial.

2) Subjects with non-zero baseline concentrations > 5% of $C_{max}$. Such data should be excluded from bioequivalence calculation (see carry-over effects below).

The above can, for immediate release formulations, be the result of subject non-compliance and an insufficient wash-out period, respectively, and should as far as possible be avoided by mouth check of subjects after intake of study medication to ensure the subjects have swallowed the study medication and by designing the study with a sufficient wash-out period. The samples from subjects excluded from the statistical analysis should still be assayed and the results listed (see Presentation of data below).

As stated in Section 3.1.4, $AUC_{(0-t)}$ should cover at least 80% of $AUC_{(0-\infty)}$. Subjects should not be excluded from the statistical analysis if $AUC_{(0-t)}$ covers less than 80% of AUC(0 -∞), but if the percentage is less than 80% in more than 20% of the observations then the validity of the study may need to be discussed. This does not apply if the sampling period is 72 h or more and $AUC_{(0-72h)}$ is used instead of $AUC_{(0-t)}$.

**Parameters to be analysed and acceptance limits**

In studies to determine bioequivalence after a single dose, the parameters to be analysed are $AUC_{(0-t)}$, or, when relevant, $AUC_{(0-72h)}$, and $C_{max}$. For these parameters the 90% confidence interval for the ratio of the test and comparator products should be contained within the acceptance interval of 80.00-125.00%. To be inside the acceptance interval the lower bound should be ≥ 80.00% when rounded to two decimal places and the upper bound should be ≤ 125.00% when rounded to two decimal places.

For studies to determine bioequivalence of immediate release formulations at steady state, $AUC_{(0-t)}$ and $C_{max,ss}$ should be analysed using the same acceptance interval as stated above.

In the rare case where urinary data has been used, $Ae_{(0-t)}$ should be analysed using the same acceptance interval as stated above for $AUC_{(0-t)}$. R max should be analysed using the same acceptance interval as for $C_{max}$.

A statistical evaluation of $t_{max}$ is not required. However, if rapid release is claimed to be clinically relevant and of importance for onset of action or is related to adverse events, there should be no apparent difference in median $T_{max}$ and its variability between test and comparator product.

In specific cases of products with a narrow therapeutic range, the acceptance interval may need to be tightened (see Section 3.1.9). Moreover, for highly variable finished pharmaceutical products the acceptance interval for $C_{max}$ may in certain cases be widened (see Section 3.1.10).

**Statistical analysis**

The assessment of bioequivalence is based upon 90% confidence intervals for the ratio of the population geometric means (test/comparator) for the parameters under consideration. This method is equivalent to two one-sided tests with the null hypothesis of bioinequivalence at the 5% significance level.

The pharmacokinetic parameters under consideration should be analysed using ANOVA. The data should be transformed prior to analysis using a logarithmic transformation. A confidence interval for the difference between formulations on the log-transformed scale is obtained from the ANOVA model. This confidence interval is then back-transformed to obtain the desired confidence interval for the ratio on the original scale. A non-parametric analysis is not acceptable.

The precise model to be used for the analysis should be pre-specified in the protocol. The statistical analysis should take into account sources of variation that can be reasonably assumed to have an effect on the response variable. The terms to be used in the ANOVA model are usually sequence, subject within sequence, period and formulation. Fixed effects, rather than random effects, should be used for all terms.

**Carry-over effects**

A test for carry-over is not considered relevant and no decisions regarding the analysis (e.g. analysis of the first period only) should be made on the basis of such a test. The potential for carry-over can be directly addressed by examination of the pre-treatment plasma concentrations in period 2 (and beyond if applicable).

If there are any subjects for whom the pre-dose concentration is greater than 5 percent of the $C_{max}$ value for the subject in that period, the statistical analysis should be performed with the data from that subject for that period excluded. In a 2-period trial this will result in the subject being removed from the analysis. The trial will no longer be considered acceptable if these exclusions result in fewer than 12 subjects being evaluable. This approach does not apply to endogenous drugs.

**Two-stage design**

It is acceptable to use a two-stage approach when attempting to demonstrate bioequivalence. An initial group of subjects can be treated and their data analysed. If bioequivalence has not been demonstrated an additional group can be recruited and the results from both groups combined in a final analysis. If this approach is adopted appropriate steps must be taken to preserve the overall type I error of the experiment and the stopping criteria should be clearly defined prior to the study.

The analysis of the first stage data should be treated as an interim analysis and both analyses conducted at adjusted significance levels (with the confidence intervals

accordingly using an adjusted coverage probability which will be higher than 90%). For example, using 94.12% confidence intervals for both the analysis of stage 1 and the combined data from stage 1 and stage 2 would be acceptable, but there are many acceptable alternatives and the choice of how much alpha to spend at the interim analysis is at the company's discretion. The plan to use a two-stage approach must be pre-specified in the protocol along with the adjusted significance levels to be used for each of the analyses.

When analyzing the combined data from the two stages, a term for stage should be included in the ANOVA model.

**Presentation of data**

All individual concentration data and pharmacokinetic parameters should be listed by formulation together with summary statistics such as geometric mean, median, arithmetic mean, standard deviation, coefficient of variation, minimum and maximum. Individual plasma concentration/time curves should be presented in linear/linear and log/linear scale. The method used to derive the pharmacokinetic parameters from the raw data should be specified. The number of points of the terminal log-linear phase used to estimate the terminal rate constant (which is needed for a reliable estimate of AUC∞) should be specified.

For the pharmacokinetic parameters that were subject to statistical analysis, the point estimate and 90% confidence interval for the ratio of the test and comparator products should be presented.

The ANOVA tables, including the appropriate statistical tests of all effects in the model, should be submitted.

The report should be sufficiently detailed to enable the pharmacokinetics and the statistical analysis to be repeated, e.g. data on actual time of blood sampling after dose, drug concentrations, the values of the pharmacokinetic parameters for each subject in each period and the randomization scheme should be provided.

Drop-out and withdrawal of subjects should be fully documented. If available, concentration data and pharmacokinetic parameters from such subjects should be presented in the individual listings, but should not be included in the summary statistics.

The bioanalytical method should be documented in a pre -study validation report. A bioanalytical report should be provided as well. The bioanalytical report should include a brief description of the bioanalytical method used and the results for all calibration standards and quality control samples. A representative number of chromatograms or other raw data should be provided covering the whole concentration range for all standard and quality control samples as well as the

specimens analysed. This should include all chromatograms from at least 20% of the subjects with QC samples and calibration standards of the runs including these subjects.

If for a particular formulation at a particular strength multiple studies have been performed some of which demonstrate bioequivalence and some of which do not, the body of evidence must be considered as a whole. Only relevant studies, as defined in Section 3.0, need be considered. The existence of a study, which demonstrates bioequivalence, does not mean that those, which do, not can be ignored. The applicant should thoroughly discuss the results and justify the claim that bioequivalence has been demonstrated. Alternatively, when relevant, a combined analysis of all studies can be provided in addition to the individual study analyses. It is not acceptable to pool together studies, which fail to demonstrate bioequivalence in the absence of a study that does.

### 3.1.9 Narrow therapeutic index drugs

In specific cases of products with a narrow therapeutic index, the acceptance interval for AUC should be tightened to 90.00-111.11%. Where $C_{max}$ is of particular importance for safety, efficacy or drug level monitoring the 90.00-111.11% acceptance interval should also be applied for this parameter. For a list of narrow therapeutic index drugs (NTIDs), refer to the table below:-

| | |
|---|---|
| Aprindine | Carbamazepine |
| Clindamycin | Clonazepam |
| Clonidine | Cyclosporine |
| Digitoxin | Digoxin |
| Disopyramide | Ethinyl Estradiol |
| Ethosuximide | Guanethidine |
| Isoprenaline | Lithium Carbonate |
| Methotrexate | Phenobarbital |
| Phenytoin | Prazosin |
| Primidone | Procainamide |
| Quinidine | Sulfonylurea compounds |
| Tacrolimus | Theophylline compounds |
| Valproic Acid | Warfarin |
| Zonisamide | Glybuzole |

### 3.1.10 Highly variable drugs or finished pharmaceutical products

Highly variable finished pharmaceutical products (HVDP) are those whose intra-subject variability for a parameter is larger than 30%. If an applicant suspects that a finished pharmaceutical product can be considered as highly variable in its rate and/or extent of absorption, a replicate cross-over design study can be carried out.

Those HVDP for which a wider difference in $C_{max}$ is considered clinically irrelevant based on a sound clinical justification can be assessed with a widened acceptance range. If this is the case the acceptance criteria for $C_{max}$ can be widened to a maximum of 69.84 – 143.19%. For the acceptance interval to be widened the bioequivalence study must be of a replicate design where it has been demonstrated that the within -subject variability for $C_{max}$ of the comparator compound in the study is >30%. The applicant should justify that the calculated intra-subject variability is a reliable estimate and that it is not the result of outliers. The request for widened interval must be prospectively specified in the protocol.

The extent of the widening is defined based upon the within-subject variability seen in the bioequivalence study using scaled-average-bioequivalence according to $[U, L] = \exp[\pm k \cdot s_{WR}]$, where U is the upper limit of the acceptance range, L is the lower limit of the acceptance range, k is the regulatory constant set to 0.760 and $s_{WR}$ is the within-subject standard deviation of the log-transformed values of $C_{max}$ of the comparator product. The table below gives examples of how different levels of variability lead to different acceptance limits using this methodology.

| Within-subject CV (%)* | Lower Limit | Upper Limit |
|---|---|---|
| 30 | 80 | 125 |
| 35 | 77.23 | 129.48 |
| 40 | 74.62 | 134.02 |
| 45 | 72.15 | 138.59 |
| ≥50 | 69.84 | 143.19 |

* $CV\,(\%) = 100\sqrt{e^{s_{WR}^2} - 1}$

The geometric mean ratio (GMR) should lie within the conventional acceptance range 80.00-125.00%.

The possibility to widen the acceptance criteria based on high intra-subject variability does not apply to AUC where the acceptance range should remain at 80.00 – 125.00% regardless of variability.

It is acceptable to apply either a 3-period or a 4-period crossover scheme in the replicate design study.

### 3.2 In vitro dissolution tests

General aspects of in vitro dissolution experiments are briefly outlined in (annexe I) including basic requirements how to use the similarity factor (*f2*-test).

### 3.2.1 In vitro dissolution tests complementary to bioequivalence studies

The results of in vitro dissolution tests at three different buffers (normally pH 1.2, 4.5 and 6.8) and the media intended for finished pharmaceutical product release (QC media), obtained with the batches of test and comparator products that were used in the bioequivalence study should be reported. Particular dosage forms like ODT (oral dispersible tablets) may require investigations using different experimental conditions. The results should be reported as profiles of percent of labelled amount dissolved versus time displaying mean values and summary statistics.

Unless otherwise justified, the specifications for the in vitro dissolution to be used for quality control of the product should be derived from the dissolution profile of the test product batch that was found to be bioequivalent to the comparator product.

In the event that the results of comparative in vitro dissolution of the biobatches do not reflect bioequivalence as demonstrated in vivo the latter prevails. However, possible reasons for the discrepancy should be addressed and justified.

### 3.2.2 In vitro dissolution tests in support of biowaiver of additional strengths

Appropriate in vitro dissolution should confirm the adequacy of waiving additional in vivo bioequivalence testing. Accordingly, dissolution should be investigated at different pH values as outlined in the previous sections (normally pH 1.2, 4.5 and 6.8) unless otherwise justified. Similarity of in vitro dissolution (**Annex II**) should be demonstrated at all conditions within the applied product series, i.e. between additional strengths and the strength(s) (i.e. batch(es)) used for bioequivalence testing.

At pH values where sink conditions may not be achievable for all strengths in vitro dissolution may differ between different strengths. However, the comparison with the respective strength of the comparator medicinal product should then confirm that this finding is active pharmaceutical ingredient rather than formulation related. In addition, the applicant could show similar profiles at the same dose (e.g. as a possibility two tablets of 5 mg versus one tablet of 10 mg could be compared). The report of a biowaiver of additional strength should follow the template format as provided in biowaiver request for additional strength (**Annex IV**).

## 3.3 Study report

### 3.3.1 Bioequivalence study report

The report of a bioavailability or bioequivalence study should follow the template format as provided in the Bioequivalence Trial Information Form (BTIF), **Annex I** in order to submit the complete documentation of its conduct and evaluation complying with GCP-rules.

The report of the bioequivalence study should give the complete documentation of its protocol, conduct and evaluation. It should be written in accordance with the ICH E3 guideline and be signed by the investigator.

Names and affiliations of the responsible investigator(s), the site of the study and the period of its execution should be stated. Audits certificate(s), if available, should be included in the report.

The study report should include evidence that the choice of the comparator medicinal product is in accordance with Selection of comparator product (**Annex V**) to be used in establishing inter changeability . This should include the comparator product name, strength, pharmaceutical form, batch number, manufacturer, expiry date and country of purchase.

The name and composition of the test product(s) used in the study should be provided. The batch size, batch number, manufacturing date and, if possible, the expiry date of the test product should be stated.

Certificates of analysis of comparator and test batches used in the study should be included in an Annex to the study report.

Concentrations and pharmacokinetic data and statistical analyses should be presented in the level of detail described above (Section 3.1.8 Presentation of data).

### 3.3.2 Other data to be included in an application

The applicant should submit a signed statement confirming that the test product has the same quantitative composition and is manufactured by the same process as the one submitted for authorization. A confirmation whether the test product is already scaled-up for production should be submitted. Comparative dissolution profiles (see Section 3.2) should be provided.

The validation report of the bioanalytical method should be included in Module 5 of the application.

Data sufficiently detailed to enable the pharmacokinetics and the statistical analysis to be repeated, e.g. data on actual times of blood sampling, drug concentrations, the values of the pharmacokinetic parameters for each subject in each period and the randomization scheme, should be available in a suitable electronic format (e.g. as comma separated and space delimited text files or Excel format) to be provided upon request.

## 3.4 Variation applications

If a product has been reformulated from the formulation initially approved or the manufacturing method has been modified in ways that may impact on the

bioavailability, an *in vivo* bioequivalence study is required, unless otherwise justified. Any justification presented should be based upon general considerations, e.g. as per BCS-Based Biowaiver (**see section 4.6**).

In cases where the bioavailability of the product undergoing change has been investigated and an acceptable level, a correlation between in vivo performance and *in vitro* dissolution has been established, the requirements for in vivo demonstration of bioequivalence can be waived if the dissolution profile *in vitro* of the new product is similar to that of the already approved medicinal product under the same test conditions as used to establish the correlation see Dissolution testing and similarity of dissolution profiles (**Annex II**).

For variations of products approved on full documentation on quality, safety and efficacy, the comparative medicinal product for use in bioequivalence and dissolution studies is usually that authorized under the currently registered formulation, manufacturing process, packaging etc.

When variations to a generic or hybrid product are made, the comparative medicinal product for the bioequivalence study should normally be a current batch of the reference medicinal product. If a valid reference medicinal product is not available on the market, comparison to the previous formulation (of the generic or hybrid product) could be accepted, if justified. For variations that do not require a bioequivalence study, the advice and requirements stated in other published regulatory guidance should be followed.

## 4.0 OTHER APPROACHES TO ASSESS THERAPEUTIC EQUIVALENCE

### 4.1 Comparative pharmacodynamics studies

Studies in healthy volunteers or patients using pharmacodynamics measurements may be used for establishing equivalence between two pharmaceuticals products. These studies may become necessary if quantitative analysis of the drug and/or metabolite(s) in plasma or urine cannot be made with sufficient accuracy and sensitivity. Furthermore, pharmacodynamics studies in humans are required if measurements of drug concentrations cannot be used as surrogate end points for the demonstration of efficacy and safety of the particular pharmaceutical product e.g., for topical products without intended absorption of the drug into the systemic circulation.

### 4.2 Comparative clinical studies

If a clinical study is considered as being undertaken to prove equivalence, the same statistical principles apply as for the bioequivalence studies. The number of patients to be included in the study will depend on the variability of the target parameters and the acceptance range, and is usually much higher than the number of subjects in

bioequivalence studies.

### 4.3 Special considerations for modified – release finished pharmaceutical products

For the purpose of these guidelines modified release products include:-

i. Delayed release
ii. Sustained release
iii. Mixed immediate and sustained release
iv. Mixed delayed and sustained release
v. Mixed immediate and delayed release

Generally, these products should:-

i. Acts as modified –release formulations and meet the label claim.
ii. Preclude the possibility of any dose dumping effects.
iii. There must be a significant difference between the performance of modified release product and the conventional release product when used as reference product.
iv. Provide a therapeutic performance comparable to the reference immediate – release formulation administered by the same route in multiple doses (of an equivalent daily amount) or to the reference modified – release formulation.
v. Produce consistent Pharmacokinetic performance between individual dosage units and
vi. Produce plasma levels which lie within the therapeutic range(where appropriate) for the proposed dosing intervals at steady state.

If all of the above conditions are not met but the applicant considers the formulation to be acceptable, justification to this effect should be provided.

#### i. Study Parameters

Bioavailability data should be obtained for all modified release finished pharmaceutical products although the type of studies required and the Pharmacokinetics parameters, which should be evaluated, may differ depending on the active ingredient involved. Factors to be considered include whether or not the formulation represents the first market entry of the active pharmaceutical ingredients, and the extent of accumulation of the drug after repeated dosing.

If formulation is the first market entry of the APIs, the products pharmacokinetic parameters should be determined. If the formulation is a second or subsequent market entry then the comparative bioavailability studies using an appropriate reference product should be performed.

### ii. Study design

Study design will be single dose or single and multiple dose based on the modified release products that are likely to accumulate or unlikely to accumulate both in fasted and non- fasting state. If the effects of food on the reference product is not known (or it is known that food affects its absorption), two separate two –way cross –over studies, one in the fasted state and the other in the fed state, may be carried out. It is known with certainty (e. g from published data) that the reference product is not affected by food, then a three-way cross – over study may be appropriate with:-

a. The reference product in the fasting;

b. The test product in the fasted state, and

c. The test product in the fed state.

### iii. Requirement for modified release formulations unlikely to accumulate

This section outlines the requirements for modified release formulations, which are used at a dose interval that is not likely to lead to accumulation in the body ($AUC_{0-v}$ /$AUC_{0-\infty} \geq 0.8$)

When the modified release product is the first marketed entry type of dosage form, the reference product should normally be the innovator immediate –release formulation. The comparison should be between a single dose of the modified release formulation and doses of the immediate – release formulation, which it is intended to replace. The latter must be administered according to the established dosing regimen.

When the release product is the second or subsequent entry on the market, comparison should be with the reference modified release product for which bioequivalence is claimed.

Studies should be performed with single dose administration in the fasting state as well as following an appropriate meal at a specified time.

The following pharmacokinetic parameters should be calculated from plasma (or relevant biological matrix) concentration of the drug and /or major metabolites(s) $AUC_{0-t}$ $AUC_{0-t}$ $AUC_{0-\infty}$, $C_{max}$ (where the comparison is with an existing modified release product) and $K_{el.}$

The 90% confidence interval calculated using log transformed data for the ratios (Test vs Reference) of the geometric mean AUC (for both $AUC_{0-t}$ and $AUC_{0-t}$) and $C_{max}$ (Where the comparison is with an existing modified release product) should

generally be within the range 80 to 125% both in the fasting state and following the administration of an appropriate meal at a specified time before taking the drug.

The Pharmacokinetic parameters should support the claimed dose delivery attributes of the modified release – dosage form.

**iv. Requirement for modified release formulations likely to accumulate**

This section outlines the requirement for modified release formulations that are used at dose intervals that are likely to lead to accumulation (AUC /AUC c o.8).

When a modified release product is the first market entry of the modified release type, the reference formulation is normally the innovators immediate – release formulation. Both a single dose and steady state doses of the modified release formulation should be compared with doses of the immediate - release formulation which it is intended to replace. The immediate – release product should be administered according to the conventional dosing regimen.

Studies should be performed with single dose administration in the fasting state as well as following an appropriate meal. In addition, studies are required at steady state. The following pharmacokinetic parameters should be calculated from single dose studies; $AUC_{0-t,}$ $AUC_{0-t,}$ $AUC_{0-\infty}$ $C_{max}$ (where the comparison is with an existing modified release product) and $K_{el}$. The following parameters should be calculated from steady state studies; $AUC_{0-t}$ $C_{max}$ $C_{min}$ $C_{pd}$, and degree of fluctuation.

When the modified release product is the second or subsequent modified release entry, single dose and steady state comparisons should normally be made with the reference modified release product for which bioequivalence is claimed.

90% confidence interval for the ration of geometric means (Test Reference drug) for AUC, $C_{max}$ and $C_{min}$ determined using log – transformed data should generally be within the range 80 to 125% when the formulation are compared at steady state.
90% confidence interval for the ration of geometric means (Test Reference drug) for $AUC_{o-t()}$,$C_{max}$, and $C_{min}$ determined using log –transferred data should generally be within the range 80 to 125% when the formulation are compared at steady state.

The Pharmacokinetic parameters should support the claimed attributes of the modified – release dosage form.

The Pharmacokinetic data may reinforce or clarify interpretation of difference in the plasma concentration data.

Where these studies do not show bioequivalence, comparative efficacy and safety data may be required for the new product.

**Pharmacodynamic studies;**

Studies in healthy volunteers or patients using pharmacodynamics parameters may be used for establishing equivalence between two pharmaceutical products. These studies may become necessary if quantitative analysis of the drug and /or metabolites (s) in plasma or urine cannot be made with sufficient accuracy and sensitivity. Furthermore, pharmacodynamic studies in humans are required if measurement of drug concentrations cannot be used as surrogate endpoints for the demonstration of efficacy and safety of the particular pharmaceutical product e.g for topical products without an intended absorption of the drug into the systemic circulation.

In case, only pharmacodynamic data is collected and provided, the applicant should outline what other methods were tried and why they were found unsuitable.

The following requirements should be recognized when planning, conducting and assessing the results from a pharmacodynamic study;

i. The response measured should be a pharmacological or therapeutically effects which is relevant to the claims of efficacy and /or safety of the drug.

ii. The methodology adopted for carrying out the study the study should be validated for precision, accuracy, reproducibility and specificity.

iii. Neither the test nor reference product should produce a maximal response in the course of the study, since it may be impossible to distinguish difference between formulations given in doses that produce such maximal responses. Investigation of dose – response relationship may become necessary.

iv. The response should be measured quantitatively under double – blind conditions and be recorded in an instrument – produced or instrument recorded fashion on a repetitive basis to provide a record of pharmacodynamic events which are suitable for plasma concentrations. If such measurement is not possible recording on visual – analogue scales may be used. In instances where data are limited to quantitative (categorized) measurement, appropriate special statistical analysis will be required.

v. Non – responders should be excluded from the study by prior screening. The criteria by which responder `-are versus non –responders are identified must be stated in the protocol.

vi. Where an important placebo effect occur comparison between products can only be made by a priori consideration of the placebo effect in the study design. This may be achieved by adding a third period/phase with placebo treatment, in the design of the study

vii. A crossover or parallel study design should be used, appropriate.

viii. When pharmacodynamic studies are to be carried out on patients, the underlying pathology and natural history of the condition should be considered in the design.

ix. There should be knowledge of the reproducibility of the base – line conditions.

x. Statistical considerations for the assessments of the outcomes are in principle, the same as in Pharmacokinetic studies.

xi. A correction for the potential non – linearity of the relationship between dose and area under the effect – time curve should be made on the basis of the outcome of the dose ranging study.

The conventional acceptance range as applicable to Pharmacokinetic studies and bioequivalence is not appropriate (too large) in most cases. This range should therefore be defined in the protocol on a case – to – case basis.

**Comparative clinical studies**

The plasma concentration time – profile data may not be suitable to assess equivalence between two formulations. Whereas in some of the cases pharmacodynamic studies can be an appropriate to for establishing equivalence , in other instances this type of study cannot be performed because of lack of meaningful pharmacodynamic parameters which can be measured and comparative clinical study has be performed in order to demonstrate equivalence between two formulations. Comparative clinical studies may also be required to be carried out for certain orally administered finished pharmaceutical products when pharmacokinetic and pharmacodynamic studies are no feasible. However, in such cases the applicant should outline what other methods were why they were found unsuitable.

If a clinical study is considered as being undertaken to prove equivalence, the appropriate statistical principles should be applied to demonstrate bioequivalence. The number of patients to be included in the study will depend on the variability of the target parameter and the acceptance range, and is usually much higher than the number of subjects in bioequivalence studies.

The following items are important and need to be defined in the protocol advance:-

a. The target parameters which usually represent relevant clinical end –points from which the intensity and the onset, if applicable and relevant, of the response are to be derived.

b. The size of the acceptance range has to be defined case taking into consideration the specific clinical conditions. These include, among others, the natural course of the disease, the efficacy of available treatment and the chosen target parameter. In contrast to bioequivalence studies (where a conventional acceptance range is applied) the size of the acceptance in clinical trials cannot be based on a general consensus on all the therapeutic clinical classes and indications.

c. The presently used statistical method is the confidence interval approach. The main concern is to rule out t Hence, a one – sided confidence interval (For efficacy and/or safety) may be appropriate. The confidence intervals can be derived from either parametric or nonparametric methods.

d. Where appropriate, a placebo leg should be included in the design.

e. In some cases, it is relevant to include safety end-points in the final comparative assessments.

### 4.4 BCS-based Biowaiver

The BCS (Biopharmaceutics Classification System)-based biowaiver approach is meant to reduce *in vivo* bioequivalence studies, *i.e.*, it may represent a surrogate for *in vivo* bioequivalence. *In vivo* bioequivalence studies may be exempted if an assumption of equivalence in *in vivo* performance can be justified by satisfactory *in vitro* data.

Applying for a BCS-based biowaiver is restricted to highly soluble active pharmaceutical ingredients with known human absorption and considered not to have a narrow therapeutic index (see Section 3.1.9). The concept is applicable to immediate release, solid pharmaceutical products for oral administration and systemic action having the same pharmaceutical form. However, it is not applicable for sublingual, buccal, and modified release formulations. For orodispersible formulations the BCS-based biowaiver approach may only be applicable when absorption in the oral cavity can be excluded.

BCS-based biowaivers are intended to address the question of bioequivalence between specific test and reference products. The principles may be used to establish bioequivalence in applications for generic medicinal products, extensions of innovator products, variations that require bioequivalence testing, and between early clinical trial products and to-be-marketed products.

## II. Summary Requirements

BCS-based biowaiver are applicable for an immediate release finished pharmaceutical product if:-

- the active pharmaceutical ingredient has been proven to exhibit high solubility and complete absorption (BCS class I; for details see Section III) and

- either very rapid (> 85 % within 15 min) or similarly rapid (85 % within 30 min ) *in vitro* dissolution characteristics of the test and reference product has been demonstrated considering specific requirements (see Section IV.1) and

- excipients that might affect bioavailability are qualitatively and quantitatively the same. In general, the use of the same excipients in similar amounts is preferred (see Section IV.2).

BCS-based biowaiver are also applicable for an immediate release finished pharmaceutical product if:-

- the active pharmaceutical ingredient has been proven to exhibit high solubility and limited absorption (BCS class III; for details see Section III) and

- very rapid (> 85 % within 15 min) *in vitro* dissolution of the test and reference product has been demonstrated considering specific requirements (see Section IV.1) and

- excipients that might affect bioavailability are qualitatively and quantitatively the same and

- other excipients are qualitatively the same and quantitatively very similar (see Section IV.2).

Generally the risks of an inappropriate biowaiver decision should be more critically reviewed (e.g. site-specific absorption, risk for transport protein interactions at the absorption site, excipient composition and therapeutic risks) for products containing BCS class III than for BCS class I active pharmaceutical ingredient.

## III. Active Pharmaceutical Ingredient

Generally, sound peer-reviewed literature may be acceptable for known compounds to describe the active pharmaceutical ingredient characteristics of importance for the biowaiver concept.

Biowaiver may be applicable when the active substance(s) in test and reference products are identical.

Biowaiver may also be applicable if test and reference contain different salts provided that both belong to BCS-class I (high solubility and complete absorption; see Sections *III.1* and *III.2*). Biowaiver is not applicable when the test product contains a different ester, ether, isomer, mixture of isomers, complex or derivative of an active substance from that of the reference product, since these differences may lead to different bioavailabilities not deducible by means of experiments used in the BCS-based biowaiver concept.

The active pharmaceutical ingredient should not belong to the group of 'narrow therapeutic index' drugs (see Section 4.1.9 on narrow therapeutic index drugs).

*III.1 Solubility*

The pH-solubility profile of the active pharmaceutical ingredient should be determined and discussed. The active pharmaceutical ingredient is considered highly soluble if the highest single dose administered as immediate release formulation(s) is completely dissolved in 250 ml of buffers within the range of pH 1 – 6.8 at 37±1 °C. This demonstration requires the investigation in at least three buffers within this range (preferably at pH 1.2, 4.5 and 6.8) and in addition at the pKa, if it is within the specified pH range. Replicate determinations at each pH condition may be necessary to achieve an unequivocal solubility classification (e.g. shake-flask method or other justified method). Solution pH should be verified prior and after addition of the active pharmaceutical ingredient to a buffer.

*III.2 Absorption*

The demonstration of complete absorption in humans is preferred for BCS-based biowaiver applications. For this purpose complete absorption is considered to be established where measured extent of absorption is ≥ 85 %. Complete absorption is generally related to high permeability.

Complete drug absorption should be justified based on reliable investigations in human. Data from either:-

- absolute bioavailability or
- mass-balance

studies could be used to support this claim.

When data from mass balance studies are used to support complete absorption, it must be ensured that the metabolites taken into account in determination of fraction absorbed are formed after absorption. Hence, when referring to total radioactivity excreted in urine, it should be ensured that there is no degradation or metabolism of the unchanged active pharmaceutical ingredient in the gastric or

intestinal fluid. Phase 1 oxidative and Phase 2 conjugative metabolism can only occur after absorption (i.e. cannot occur in the gastric or intestinal fluid). Hence, data from mass balance studies support complete absorption if the sum of urinary recovery of parent compound and urinary and faecal recovery of Phase 1 oxidative and Phase 2 conjugative drug metabolites account for ≥ 85 % of the dose.

In addition highly soluble active pharmaceutical ingredients with incomplete absorption, i.e. BCS-class III compounds, could be eligible for a biowaiver provided certain prerequisites are fulfilled regarding product composition and *in vitro* dissolution (see also Section *IV.2* Excipients). The more restrictive requirements will also apply for compounds proposed to be BCS class I but where complete absorption could not convincingly be demonstrated.

Reported bioequivalence between aqueous and solid formulations of a particular compound administered via the oral route may be supportive as it indicates that absorption limitations due to (immediate release) formulation characteristics may be considered negligible. Well performed *in vitro* permeability investigations including reference standards may also be considered supportive to *in vivo* data.

## IV. Finished pharmaceutical product

### *IV.1 In vitro Dissolution*

#### *IV.1.1 General Aspects*

Investigations related to the medicinal product should ensure immediate release properties and prove similarity between the investigative products, i.e. test and reference show similar *in vitro* dissolution under physiologically relevant experimental pH conditions. However, this does not establish an *in vitro*/*in vivo* correlation. *In vitro* dissolution should be investigated within the range of pH 1 – 6.8 (at least pH 1.2, 4.5, and 6.8). Additional investigations may be required at pH values in which the drug substance has minimum solubility. The use of any surfactant is not acceptable.

Test and reference products should meet requirements as outlined in Section 3.1.2 of the main guideline text. In line with these requirements it is advisable to investigate more than one single batch of the test and reference products.
Comparative *in vitro* dissolution experiments should follow current compendial standards. Hence, thorough description of experimental settings and analytical methods including validation data should be provided. It is recommended to use 12 units of the product for each experiment to enable statistical evaluation. Usual experimental conditions are e.g.:-

- Apparatus: paddle or basket
- Volume of dissolution medium: 900 ml or less

- Temperature of the dissolution medium: 37±1 °C
- Agitation:
    - paddle apparatus - usually 50 rpm
    - basket apparatus - usually 100 rpm
- Sampling schedule: e.g. 10, 15, 20, 30 and 45 min
- Buffer: pH 1.0 – 1.2 (usually 0.1 N HCl or SGF without enzymes), pH 4.5, and pH 6.8 (or SIF without enzymes); (pH should be ensured throughout the experiment; Ph.Eur. buffers recommended)
- Other conditions: no surfactant; in case of gelatin capsules or tablets with gelatin coatings the use of enzymes may be acceptable.

Complete documentation of *in vitro* dissolution experiments is required including a study protocol, batch information on test and reference batches, detailed experimental conditions, validation of experimental methods, individual and mean results and respective summary statistics.

*IV.1.2 Evaluation of in vitro dissolution results*

Finished pharmaceutical products are considered 'very rapidly' dissolving when more than 85 % of the labelled amount is dissolved within 15 min. In cases where this is ensured for the test and reference product the similarity of dissolution profiles may be accepted as demonstrated without any mathematical calculation.

Absence of relevant differences (similarity) should be demonstrated in cases where it takes more than 15 min but not more than 30 min to achieve almost complete (at least 85 % of labelled amount) dissolution. *F2*-testing (see Annex I) or other suitable tests should be used to demonstrate profile similarity of test and reference. However, discussion of dissolution profile differences in terms of their clinical/therapeutical relevance is considered inappropriate since the investigations do not reflect any *in vitro/in vivo* correlation.

*IV.2 Excipients*

Although the impact of excipients in immediate release dosage forms on bioavailability of highly soluble and completely absorbable active pharmaceutical ingredients (i.e., BCS-class I) is considered rather unlikely it cannot be completely excluded. Therefore, even in the case of class I drugs it is advisable to use similar amounts of the same excipients in the composition of test like in the reference product.

If a biowaiver is applied for a BCS-class III active pharmaceutical ingredient excipients have to be qualitatively the same and quantitatively very similar in order to exclude different effects on membrane transporters.

As a general rule, for both BCS-class I and III APIs well-established excipients in usual amounts should be employed and possible interactions affecting drug bioavailability and/or solubility characteristics should be considered and discussed. A description of the function of the excipients is required with a justification whether the amount of each excipient is within the normal range. Excipients that might affect bioavailability, like e.g. sorbitol, mannitol, sodium lauryl sulfate or other surfactants, should be identified as well as their possible impact on:-

- gastrointestinal motility
- susceptibility of interactions with the active pharmaceutical ingredient (e.g. complexation)
- drug permeability
- interaction with membrane transporters

Excipients that might affect bioavailability should be qualitatively and quantitatively the same in the test product and the reference product.

*V. Fixed Combinations (FCs)*

BCS-based biowaiver are applicable for immediate release FC products if all active substances in the FC belong to BCS-class I or III and the excipients fulfil the requirements outlined in Section IV.2. Otherwise *in vivo* bioequivalence testing is required.

Application form for BCS biowaiver (**Annex III**)

## 5. BIOEQUIVALENCE STUDY REQUIREMENTS FOR DIFFERENT DOSAGE FORMS

Although this guideline concerns immediate release formulations, this section provides some general guidance on the bioequivalence data requirements for other types of formulations and for specific types of immediate release formulations.

When the test product contains a different salt, ester, ether, isomer, mixture of isomers, complex or derivative of an active substance than the reference medicinal product, bioequivalence should be demonstrated in *in vivo* bioequivalence studies. However, when the active substance in both test and reference products is identical (or contain salts with similar properties as defined in Section III), *in vivo* bioequivalence studies may in some situations not be required as described below.

**Oral immediate release dosage forms with systemic action**

For dosage forms such as tablets, capsules and oral suspensions, bioequivalence studies are required unless a biowaiver is applicable. For orodispersable tablets and oral solutions specific recommendations apply, as detailed below.

***Orodispersible tablets***

An orodispersable tablet (ODT) is formulated to quickly disperse in the mouth. Placement in the mouth and time of contact may be critical in cases where the active substance also is dissolved in the mouth and can be absorbed directly via the buccal mucosa. Depending on the formulation, swallowing of the e.g. coated substance and subsequent absorption from the gastrointestinal tract also will occur. If it can be demonstrated that the active substance is not absorbed in the oral cavity, but rather must be swallowed and absorbed through the gastrointestinal tract, then the product might be considered for a BCS based biowaiver (**see section 4.6).** If this cannot be demonstrated, bioequivalence must be evaluated in human studies.

If the ODT test product is an extension to another oral formulation, a 3-period study is recommended in order to evaluate administration of the orodispersible tablet both with and without concomitant fluid intake. However, if bioequivalence between ODT taken without water and reference formulation with water is demonstrated in a 2-period study, bioequivalence of ODT taken with water can be assumed.

If the ODT is a generic/hybrid to an approved ODT reference medicinal product, the following recommendations regarding study design apply:-

- if the reference medicinal product can be taken with or without water, bioequivalence should be demonstrated without water as this condition best resembles the intended use of the formulation. This is especially important if the substance may be dissolved and partly absorbed in the oral cavity. If bioequivalence is demonstrated when taken without water, bioequivalence when taken with water can be assumed.
- if the reference medicinal product is taken only in one way (e.g. only with water), bioequivalence should be shown in this condition (in a conventional two-way crossover design).
- if the reference medicinal product is taken only in one way (e.g. only with water), and the test product is intended for additional ways of administration (e.g. without water), the conventional and the new method should be compared with the reference in the conventional way of administration (3 treatment, 3 period, 6 sequence design).

In studies evaluating ODTs without water, it is recommended to wet the mouth by swallowing 20 ml of water directly before applying the ODT on the tongue. It is recommended not to allow fluid intake earlier than 1 hour after administration.

Other oral formulations such as orodispersible films, buccal tablets or films, sublingual tablets and chewable tablets may be handled in a similar way as for ODTs. Bioequivalence studies should be conducted according to the recommended use of the product.

## ANNEX I: PRESENTATION OF BIOPHARMACEUTICAL AND BIO-ANALYTICAL DATA IN MODULE 2.7.1

### 1. Introduction

The objective of CTD Module 2.7.1 is to summarize all relevant information in the product dossier with regard to bioequivalence studies and associated analytical methods.

This Annex contains a set of template tables to assist applicants in the preparation of Module 2.7.1 providing guidance with regard to data to be presented. Furthermore, it is anticipated that a standardized presentation will facilitate the evaluation process. The use of these template tables is therefore recommended to applicants when preparing Module 2.7.1. This Annex is intended for generic applications. Furthermore, if appropriate then it is also recommended to use these template tables in other applications such as variations, fixed combinations, extensions and hybrid applications.

### 2. Instructions for completion and submission of the tables

The tables should be completed only for the pivotal studies, as identified in the application dossier in accordance with section 3.1 of the Bioequivalence guideline. If there is more than one pivotal bioequivalence study, then individual tables should be prepared for each study. In addition, the following instructions for the tables should be observed:

Tables in Section 3 should be completed separately for each analyte per study. If there is more than one test product then the table structure should be adjusted.

Tables in Section 3 should only be completed for the method used in confirmatory (pivotal) bioequivalence studies. If more than one analyte was measured then Table 3.1 and potentially Table 3.3 should be completed for each analyte.

In general, applicants are encouraged to use cross-references and footnotes for adding additional information. Fields that does not apply should be completed as "Not applicable" together with an explanatory footnote if needed.

In addition, each section of the template should be cross-referenced to the location of supporting documentation or raw data in the application dossier.
The tables should not be scanned copies and their content should be searchable. It is strongly recommended that applicants provide Module 2.7.1 also in Word (.doc).

**BIOEQUIVALENCE TRIAL INFORMATION FORM**

**Table 1.1 Test and reference product information**

| **Product Characteristics** | **Test product** | **Reference Product** |
|---|---|---|
| Name | | |
| Strength | | |
| Dosage form | | |
| Manufacturer | | |
| Batch number | | |
| Batch size (Biobatch) | | |
| Measured content(s)[1] (% of label claim) | | |
| Commercial Batch Size | | |
| Expiry date (Retest date) | | |
| Location of Certificate of Analysis | <Vol/page, link> | <Vol/page, link> |
| Country where the reference product is purchased from: | | |
| This product was used in the following trials: | <Study ID(s)> | <Study ID(s)> |

Note: if more than one batch of the Test or Reference products were used in the bioequivalence trials then fill out Table 2.1 for each Test/Reference batch combination.

**1.2 Study Site(s) of <Study ID>**

| | Name | Address | Authority Inspection | |
|---|---|---|---|---|
| | | | Year | |
| Clinical Study Site | | | | Clinical Study Site |
| Bioanalytical Study Site | | | | Bioanalytical Study Site |
| PK and Statistical Analysis | | | | PK and Statistical Analysis |
| Sponsor of the study | | | | Sponsor of the study |

**Table 1.3 Study description of <Study ID>**

Study Title:

| |
|---|
| Report Location: <vol/page, link><br>Study Periods<br>Clinical: <DD Month YYYY> - <DD Month YYYY> |

| | |
|---|---|
| Bioanalytical: | <DD Month YYYY> - <DD Month YYYY> |
| Design | |
| Dose: | |
| Single/Multiple dose: | |
| Number of periods: | |
| Two-stage design: | (yes/no) |
| Fasting/ Fed: | |
| Number of subjects | |
| - dosed: | <##> |
| - completed the study: | <##> |
| - included in the final statistical analysis of AUC: | <##> |
| - included in the final statistical analysis of Cmax: | |

Fill out Tables 2.2 and 2.3 for each study.

**2. Results**

**Table 2.1 Pharmacokinetic data for <analyte> in <Study ID>**

| Pharmacokinetic parameter | [4]Arithmetic Means (±SD) | |
|---|---|---|
| | Test product | Reference Product |
| $AUC_{(0-t)}$ [1] | | |
| $AUC_{(0-\infty)}$ [2] | | |
| Cmax | | |
| tmax[3] | | |

[1] $AUC_{(0-72h)}$ can be reported instead of $AUC_{(0-t)}$, in studies with a sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release. products.

[2] $AUC_{(0-\infty)}$ does not need to be reported when $AUC_{(0-72h)}$ is reported instead of $AUC_{(0-t)}$.

[3] Median (Min, Max)

[4] Arithmetic Means (±SD) may be substituted by Geometric Mean (±CV%)

**Table 2.2 Additional pharmacokinetic data for <analyte> in <Study ID>**

| **Plasma concentration curves where** | **Related information** |
|---|---|
| - $AUC_{(0-t)}/AUC_{(0-\infty)}<0.8$[1] | <subject ID, period #, F[2]> |
| - Cmax is the first point | <subject ID, period #, F> |
| - Pre-dose sample > 5% Cmax | <subject ID, period #, F, pre-dose concentration> |

[1] Only if the last sampling point of $AUC_{(0-t)}$ is less than 72h

[2] F = T for the Test formulation or F = R for the Reference formulation

**Table 2.3 Bioequivalence evaluation of <analyte> in <Study ID>**

| **Pharmacokinetic parameter** | **Geometric Mean Ratio Test/Ref** | **Confidence Intervals** | **CV%[1]** |
|---|---|---|---|
| $AUC^{2}_{(0-t)}$ | | | |
| Cmax | | | |

[1]Estimated from the Residual Mean Squares. For replicate design studies report the within-subject CV% using only the reference product data.

[2] In some cases $AUC_{(0-72)}$

**Instructions**
Fill out Tables 3.1-3.3 for each relevant analyte.

**3. Bio-analytics**

**Table 3.1 Bio-analytical method validation**

| | | |
|---|---|---|
| Analytical Validation Report Location(s) | <Study Code><br><vol/page, link> | |
| This analytical method was used in the following studies: | <Study IDs> | |
| Short description of the method | <e.g. HPLC/MS/MS, GC/MS, Ligand binding> | |
| Biological matrix | <e.g. Plasma, Whole Blood, Urine> | |
| Analyte<br>Location of product certificate | <Name>,<br><vol/page, link)> | |
| Internal standard (IS)[1]<br>Location of product certificate | <Name><br><vol/page, link> | |
| Calibration concentrations (Units) | | |
| Lower limit of quantification (Units) | <LLOQ>, <Accuracy%>, <Precision%> | |
| QC concentrations (Units) | | |
| Between-run accuracy | <Range or by QC> | |
| Between-run precision | <Range or by QC> | |
| Within-run accuracy | <Range or by QC> | |
| Within-run precision | <Range or by QC> | |
| Matrix Factor (MF) (all QC)[1]<br>IS normalized MF (all QC)[1]<br>C.V.% of IS normalized MF (all QC)[1] | Low QC<br><Mean><br><Mean><br><C.V.%> | High QC<br><Mean><br><Mean><br><C.V.%> |

| | | |
|---|---|---|
| % of QCs with >85% and <115% n.v.[1,4]<br>% matrix lots with mean <80% or>120% n.v[1,4] | <%><br><%> | <%><br><%> |
| Long term stability of the stock solution and working solutions[2] (Observed change %), | Confirmed up to <Time> at <°C><br><%, Range or by QC> | |
| Short term stability in biological matrix at room temperature or at sample processing temperature. (Observed change %) | Confirmed up to <Time><br><%, Range or by QC> | |
| Long term stability in biological matrix (Observed change %)<br>Location | Confirmed up to <Time> at < °C><br><%, Range or by QC><br><vol/page, link> | |
| Autosampler storage stability (Observed change %) | Confirmed up to <Time><br><%, Range or by QC> | |
| Post-preparative stability (Observed change %) | Confirmed up to <Time><br><%, Range or by QC> | |
| Freeze and thaw stability (Observed change %) | <-Temperature °C, # cycles, ><br><Range or by QC> | |
| Dilution integrity | Concentration diluted <X-fold><br>Accuracy <%> Precision <%> | |
| Long term stability of the stock solution and working solutions[2] (Observed change %), | Confirmed up to <Time> at <°C><br><%, Range or by QC> | |
| Short term stability in biological matrix at room temperature or at sample processing temperature. (Observed change %) | Confirmed up to <Time><br><%, Range or by QC> | |
| Long term stability in biological matrix (Observed change %)<br>Location | Confirmed up to <Time> at < °C><br><%, Range or by QC><br><vol/page, link> | |
| Autosampler storage stability (Observed change %) | Confirmed up to <Time><br><%, Range or by QC> | |
| Post-preparative stability (Observed change %) | Confirmed up to <Time><br><%, Range or by QC> | |
| Freeze and thaw stability (Observed change %) | <-Temperature °C, # cycles, ><br><Range or by QC> | |
| Dilution integrity | Concentration diluted <X-fold><br>Accuracy <%> Precision <%> | |
| Partial validation[3]<br>Location(s) | <Describe shortly the reason of revalidation(s)><br><vol/page, link> | |
| Cross validation(s) [3] | <Describe shortly the reason of cross- | |

| | |
|---|---|
| Location(s) | validations><br><vol/page, link> |

[1]Might not be applicable for the given analytical method

[2] Report short term stability results if no long term stability on stock and working solution are available

[3] These rows are optional. Report any validation study which was completed after the initial validation study,

[4] n.v. = nominal value

**Instruction**

Many entries in Table 4.1 are applicable only for chromatographic and not ligand binding methods. Denote with NA if an entry is not relevant for the given assay. Fill out Table 4.1 for each relevant analyte.

**Table 3.2 Storage period of study samples**

| Study ID[1] and analyte | Longest storage period |
|---|---|
| | <#> days at temperature < $C^o$ > |
| | <#> days at temperature < $C^o$ > |

[1] Only pivotal trials

**Table 3.3 Sample analysis of <Study ID>**

| Analyte | <Name> |
|---|---|
| Total numbers of collected samples | <#> |
| Total number of samples with valid results | <#> |
| Total number of reassayed samples[1,2] | <#> |
| Total number of analytical runs[1] | <#> |
| Total number of valid analytical runs[1] | <#> |
| **Incurred sample reanalysis** | |
| Number of samples | <#> |
| Percentage of samples where the difference between the two values was less than 20% of the mean for chromatographic assays or less than 30% for ligand binding assays | <%> |

Without incurred samples

[2] Due to other reasons than not valid run

**Instructions**

Fill out Table 3.3 for each relevant analyte.

## ANNEX II: DISSOLUTION TESTING AND SIMILARITY OF DISSOLUTION PROFILES

### General aspects of dissolution testing as related to bioavailability

During the development of a medicinal product dissolution test is used as a tool to identify formulation factors that are influencing and may have a crucial effect on the bioavailability of the drug. As soon as the composition and the manufacturing process are defined a dissolution test is used in the quality control of scale-up and of production batches to ensure both batch-to-batch consistency and that the dissolution profiles remain similar to those of pivotal clinical trial batches. Furthermore, in certain instances a dissolution test can be used to waive a bioequivalence study. Therefore, dissolution studies can serve several purposes:-

(a) Testing on product quality:-

- To get information on the test batches used in bioavailability/bioequivalence studies and pivotal clinical studies to support specifications for quality control.
- To be used as a tool in quality control to demonstrate consistency in manufacture.
- To get information on the reference product used in bioavailability/bioequivalence studies and pivotal clinical studies.

(b) Bioequivalence surrogate inference

- To demonstrate in certain cases similarity between different formulations of an active substance and the reference medicinal product (biowaivers e.g., variations, formulation changes during development and generic medicinal products; see Section 3.2.
- To investigate batch to batch consistency of the products (test and reference) to be used as basis for the selection of appropriate batches for the in vivo study.

Test methods should be developed product related based on general and/or specific pharmacopoeial requirements. In case those requirements are shown to be unsatisfactory and/or do not reflect the in vivo dissolution (i.e. biorelevance) alternative methods can be considered when justified that these are discriminatory and able to differentiate between batches with acceptable and non-acceptable performance of the product in vivo. Current state-of-the -art information including the interplay of characteristics derived from the BCS classification and the dosage form must always be considered.

Sampling time points should be sufficient to obtain meaningful dissolution profiles, and at least every 15 minutes. More frequent sampling during the period of greatest

change in the dissolution profile is recommended. For rapidly dissolving products, where complete dissolution is within 30 minutes, generation of an adequate profile by sampling at 5- or 10-minute intervals may be necessary.

If an active substance is considered highly soluble, it is reasonable to expect that it will not cause any bioavailability problems if, in addition, the dosage system is rapidly dissolved in the physiological pH-range and the excipients are known not to affect bioavailability. In contrast, if an active substance is considered to have a limited or low solubility, the rate-limiting step for absorption may be dosage form dissolution. This is also the case when excipients are controlling the release and subsequent dissolution of the active substance. In those cases a variety of test conditions is recommended and adequate sampling should be performed.

**Similarity of dissolution profiles**

Dissolution profile similarity testing and any conclusions drawn from the results (e.g. justification for a biowaiver) can be considered valid only if the dissolution profile has been satisfactorily characterised using a sufficient number of time points.

For immediate release formulations, further to the guidance given in Section 1 above, comparison at 15 min is essential to know if complete dissolution is reached before gastric emptying.

Where more than 85% of the drug is dissolved within 15 minutes, dissolution profiles may be accepted as similar without further mathematical evaluation.
In case more than 85% is not dissolved at 15 minutes but within 30 minutes, at least three time points are required: the first time point before 15 minutes, the second one at 15 minutes and the third time point when the release is close to 85%.

For modified release products, the advice given in the relevant guidance should be followed.

Dissolution similarity may be determined using the $f2$ statistic as follows:

$$f_2 = 50 \cdot \log\left[\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{t=n}[\overline{R}(t) - \overline{T}(t)]^2}{n}}}\right]$$

In this equation $f2$ is the similarity factor, n is the number of time points, R(t) is the mean percent reference drug dissolved at time t after initiation of the study; T(t) is

the mean percent test drug dissolved at time t after initiation of the study. For both the reference and test formulations, percent dissolution should be determined.

The evaluation of the similarity factor is based on the following conditions:

- A minimum of three time points (zero excluded)
- The time points should be the same for the two formulations
- Twelve individual values for every time point for each formulation
- Not more than one mean value of > 85% dissolved for any of the formulations.
- The relative standard deviation or coefficient of variation of any product should be less than 20% for the first point and less than 10% from second to last time point.

An f2 value between 50 and 100 suggests that the two dissolution profiles are similar.

When the $f2$ statistic is not suitable, then the similarity may be compared using model-dependent or model-independent methods e.g. by statistical multivariate comparison of the parameters of the Weibull function or the percentage dissolved at different time points.

Alternative methods to the $f2$ statistic to demonstrate dissolution similarity are considered acceptable, if statistically valid and satisfactorily justified.

The similarity acceptance limits should be pre-defined and justified and not be greater than a 10% difference. In addition, the dissolution variability of the test and reference product data should also be similar; however, a lower variability of the test product may be acceptable.

Evidence that the statistical software has been validated should also be provided.
A clear description and explanation of the steps taken in the application of the procedure should be provided, with appropriate summary tables.

## ANNEX III: BCS BIOWAIVER APPLICATION FORM

This application form is designed to facilitate information exchange between the Applicant and the EAC-NMRA if the Applicant seeks to waive bioequivalence studies, based on the Biopharmaceutics Classification System (BCS). This form is not to be used, if a biowaiver is applied for additional strength(s) of the submitted product(s), in which situation a separate "*Biowaiver Application Form: Additional Strengths*" should be used.

General Instructions:

- Please review all the instructions thoroughly and carefully prior to completing the current Application Form.
- Provide as much detailed, accurate and final information as possible.
- Please enter the data and information directly following the greyed areas.
- Please enclose the required documentation in full and state in the relevant sections of the Application Form the exact location (Annex number) of the appended documents.
- Please provide the document as an MS Word file.
- Do not paste snap-shots into the document.
- The appended electronic documents should be clearly identified in their file names, which should include the product name and Annex number.
- Before submitting the completed Application Form, kindly check that you have provided all requested information and enclosed all requested documents.

### 1.0 Administrative data

### 1.1 Trade name of the test product

| **1.2 INN of active ingredient(s)** |
|---|
| < *Please enter information here* > |
| **1.3 Dosage form and strength** |
| < *Please enter information here* > |
| **1.4 Product NMRA Reference number** *(if product dossier has been accepted for assessment)* |
| < *Please enter information here* > |

| 1.5 | Name of applicant and official address |
|---|---|
| < *Please enter information here* > | |

| 1.6 | Name of manufacturer of finished product and full physical address of the manufacturing site |
|---|---|
| < *Please enter information here* > | |

| 1.7 | Name and address of the laboratory or Contract Research Organisation(s) where the BCS-based biowaiver dissolution studies were conducted. |
|---|---|
| < *Please enter information here* > | |

I, the undersigned, certify, that the information provided in this application and the attached document(s) is correct and true

Signed on behalf of ***<company>***

_____ (Date)

_____ (Name and title)

**2.0 Test product**

| 2.1 | Tabulation of the composition of the formulation(s) proposed for marketing and those used for comparative dissolution studies |
|---|---|
| • Please state the location of the master formulae in the specific part of the dossier) of the submission.<br>• Tabulate the composition of each product strength using the table 2.1.1<br>• For solid oral dosage forms the table should contain only the ingredients in tablet core or contents of a capsule. A copy of the table should be filled in for the film coating/hard gelatine capsule, if any.<br>• Biowaiver batches should be at least of pilot scale (10% of production scale or 100,000 capsules or tablets whichever is greater) and manufacturing method should be the same as for production scale. | |

**Please note:** If the formulation proposed for marketing and those used for comparative dissolution studies are not identical, copies of this table should be

filled in for each formulation with clear identification in which study the respective formulation was used

| **2.1.1 Composition of the batches used for comparative dissolution studies** | | | | |
|---|---|---|---|---|
| Batch number | | | | |
| Batch size (number of unit doses) | | | | |
| Date of manufacture | | | | |
| Comments, if any | | | | |
| Comparison of unit dose compositions<br>(duplicate this table for each strength, if compositions are different) | | | | |
| Ingredients (Quality standard) | Unit dose (mg) | Unit dose (%) | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| Equivalence of the compositions or justified differences | | | | |

**2.2 Potency (measured content) of test product as a percentage of label claim as per validated assay method**

This information should be cross-referenced to the location of the Certificate of Analysis (CoA) in this biowaiver submission.

*<< Please enter information here >>*

COMMENTS FROM REVIEW OF SECTION 2.0 – *OFFICIAL USE ONLY*

## 3.0 Comparator product

**3.1 Comparator product**

Please enclose a copy of product labelling (summary of product characteristics), as authorized in country of purchase, and translation into English, if appropriate.

| **3.2 Name and manufacturer of the comparator product (Include full physical address of the manufacturing site)** |
|---|
| < *Please enter information here* > |

| **3.3 Qualitative (and quantitative, if available) information on the composition of the comparator product** |
|---|
| Please tabulate the composition of the comparator product based on available information and state the source of this information. |

| **3.3.1 Composition of the comparator product used in dissolution studies** | | |
|---|---|---|
| Batch number | | |
| Expiry date | | |
| Comments, if any | | |
| Ingredients and reference standards used | Unit dose (mg) | Unit dose (%) |
| | | |
| | | |
| | | |
| | | |
| | | |

| **3.4 Purchase, shipment and storage of the comparator product** |
|---|
| Please attach relevant copies of documents (e.g. receipts) proving the stated conditions. |

| << *Please enter information here* >> |
|---|

| **3.5 Potency (measured content) of the comparator product as a percentage of label claim, as measured by the same laboratory under the same conditions as the test product.** |
|---|
| This information should be cross-referenced to the location of the Certificate of Analysis (CoA) in this biowaiver submission. |

| << *Please enter information here* >> |
|---|

| COMMENTS FROM REVIEW OF SECTION 3.0 – *OFFICIAL USE ONLY* |
| --- |
| |

## 4.0 Comparison of test and comparator products

### 4.1 Formulation

#### 4.1.1 Identify any excipients present in either product that are known to impact on *in vivo* absorption processes

A literature-based summary of the mechanism by which these effects are known to occur should be included and relevant full discussion enclosed, if applicable.

*<< Please enter information here >>*

#### 4.1.2 Identify all qualitative (and quantitative, if available) differences between the compositions of the test and comparator products

The data obtained and methods used for the determination of the quantitative composition of the comparator product as required by the guidance documents should be summarized here for assessment.

*<< Please enter information here >>*

#### 4.1.3 Provide a detailed comment on the impact of any differences between the compositions of the test and comparator products with respect to drug release and in vivo absorption

*<< Please enter information here >>*

| COMMENTS FROM REVIEW OF SECTION 4.0 – *OFFICIAL USE ONLY* |
| --- |
| |

**5.0 Comparative in vitro dissolution**

Information regarding the comparative dissolution studies should be included below to provide adequate evidence supporting the biowaiver request. Comparative dissolution data will be reviewed during the assessment of the Quality part of the dossier.

Please state the location of:

- the dissolution study protocol(s) in this biowaiver application
- the dissolution study report(s) in this biowaiver application
- the analytical method validation report in this biowaiver application

*<< Please enter information here >>*

**5.1 Summary of the dissolution conditions and method described in the study report(s)**

Summary provided below should include the composition, temperature, volume, and method of de-aeration of the dissolution media, the type of apparatus employed, the agitation speed(s) employed, the number of units employed, the method of sample collection including sampling times, sample handling, and sample storage. Deviations from the sampling protocol should also be reported.

**5.1.1 Dissolution media: Composition, temperature, volume, and method of de-aeration**

*<< Please enter information here >>*

**5.1.2 Type of apparatus and agitation speed(s) employed**

*<< Please enter information here >>*

**5.1.3 Number of units employed**

*<< Please enter information here >>*

**5.1.4 Sample collection: method of collection, sampling times, sample handling and storage**

*<< Please enter information here >>*

**5.1.5 Deviations from sampling protocol**

*<< Please enter information here >>*

**5.2 Summarize the results of the dissolution study(s)**

Please provide a tabulated summary of individual and mean results with %CV, graphic summary, and any calculations used to determine the similarity of profiles **for each set of experimental conditions**.

*<< Please enter information here >>*

**5.3 Provide discussions and conclusions taken from dissolution study(s)**

Please provide a summary statement of the studies performed.

*<< Please enter information here >>*

COMMENTS FROM REVIEW OF SECTION 5.0: – *OFFICIAL USE ONLY*

## 6.0 Quality assurance

**6.1 Internal quality assurance methods**

Please state location in this biowaiver application where internal quality assurance methods and results are described for each of the study sites.

*<< Please enter information here >>*

**6.2 Monitoring, Auditing, Inspections**

Provide a list of all auditing reports of the study, and of recent inspections of study sites by regulatory agencies. State locations in this biowaiver application of the respective reports for each of the study sites e.g., analytical laboratory, laboratory where dissolution studies were performed.

*<< Please enter information here >>*

COMMENTS FROM REVIEW OF SECTION 6.0 – *OFFICIAL USE ONLY*

CONCLUSIONS AND RECOMMENDATIONS – *OFFICIAL USE ONLY*

**ANNEX IV: BIOWAIVER REQUEST FOR ADDITIONAL STRENGTHS**

**Instructions**

Fill this table only if bio-waiver is requested for additional strengths besides the strength tested in the bioequivalence study. Only the mean percent dissolution values should be reported but denote the mean by star (*) if the corresponding RSD is higher than 10% except the first point where the limit is 20%. Expand the table with additional columns according to the collection times. If more than 3 strengths are requested then add additional rows. f2 values should be computed relative to the strength tested in the bioequivalence study. Justify in the text if not f2 but an alternative method was used

**Table 1.1 Qualitative and quantitative composition of the Test product**

| Ingredient | Function | Strength (Label claim) | | | | | |
|---|---|---|---|---|---|---|---|
| | | XX mg (Production Batch Size) | | XX mg (Production Batch Size) | | XX mg (Production Batch Size) | |
| Core | | Quantity per unit | %* | Quantity per unit | %* | Quantity per unit | %* |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| Total | | | 100 | | 100 | | 100 |
| | | | | | | | |
| Coating | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| Total | | | 100 | | 100 | | 100 |

**each ingredient expressed as a percentage (w/w) of the total core or coating weight or w/v % for solutions*

**Instructions**

Include the composition of all strengths. Add additional columns if necessary.

| Dissolution media | Collection Times (minutes or hours) | | | | | | f2 |
|---|---|---|---|---|---|---|---|
| | 5 | 15 | 20 | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Strength 1<br># of units<br># Batch no | pH | | | | | | | |
| | pH | | | | | | | |
| | pH | | | | | | | |
| | Q.C<br>Medium | | | | | | | |
| Strength 2<br># of units<br># Batch no | pH | | | | | | | |
| | pH | | | | | | | |
| | pH | | | | | | | |
| | Q.C<br>Medium | | | | | | | |
| Strength 2<br># of units<br># Batch no | pH | | | | | | | |
| | pH | | | | | | | |
| | pH | | | | | | | |
| | Q.C<br>Medium | | | | | | | |

[1] Only if the medium intended for drug product release is different from the buffers above.

## ANNEX V: SELECTION OF A COMPARATOR PRODUCT TO BE USED IN ESTABLISHING INTERCHANGEABILITY

### I Introduction

This annex is intended to provide applicants with guidance with respect to selecting an appropriate comparator product to be used to prove therapeutic equivalence (i.e. interchangeability) of their product to an existing medicinal product(s).

### II Comparator product

Is a pharmaceutical product with which the generic product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product for which efficacy, safety and quality have been established.

### III Guidance on selection of a comparator product

General principles for the selection of comparator products are described in the EAC guidelines on therapeutic equivalence requirements.

The innovator pharmaceutical product, which was first authorized for marketing, is the most logical comparator product to establish interchangeability, because its quality, safety and efficacy has been fully assessed and documented in pre-marketing studies and post-marketing monitoring schemes.

A generic pharmaceutical product should not be used as a comparator as long as an innovator pharmaceutical product is available, because this could lead to progressively less reliable similarity of future multisource products and potentially to a lack of interchangeability with the innovator.

Comparator products should be purchased from a well regulated market with stringent regulatory authority, i.e. from countries participating in the International Conference on Harmonization (ICH)[1]

The applicant has the following options which are listed in order of preference:

1. To choose an innovator product;

2. To choose a product which is approved and has been on the market in any of the ICH and associated countries for more than five years;

3. To choose the WHO recommended comparator product (as presented in the developed lists);

In case no recommended comparator product is identified; or in case the EAC recommended comparator product cannot be located in a well regulated market with stringent regulatory authority as noted above, the applicant should consult EAC regarding the choice of comparator before starting any studies.

## IV Origin of the comparator product

Comparator products should be purchased from a well regulated market with stringent regulatory authority, i.e. from countries participating in the International Conference on Harmonization (ICH)[1]. Within the submitted dossier, the country of origin of the comparator product should be reported together with lot number and expiry date, as well as results of pharmaceutical analysis to prove pharmaceutical equivalence.

Further in order to prove the origin of the comparator product the applicant must present all of the following documents:-

1. Copy of the comparator product labelling. The name of the product, name and address of the manufacturer, batch number, and expiry date should be clearly visible on the labelling.

2. Copy of the invoice from the distributor or company from which the comparator product was purchased. The address of the distributor must be clearly visible on the invoice.

3. Documentation verifying the method of shipment and storage conditions of the comparator product from the time of purchase to the time of study initiation.

4. A signed statement certifying the authenticity of the above documents and that the comparator product was purchased from the specified national market. The company executive responsible for the application for registration of pharmaceutical product should sign the certification.

In case the invited product has a different dose compared to the available acceptable comparator product, it is not always necessary to carry out a bioequivalence study at the same dose level; if the active substance shows linear pharmacokinetics, extrapolation may be applied by dose normalization.

The bioequivalence of fixed-dose combination (FDC) should be established following the same general principles. The submitted FDC product should be compared with the respective innovator FDC product. In cases when no innovator FDC product is available on the market, individual component products administered in loose combination should be used as a comparator.